Summary Report

New Medical Technology: Experimental or State-of-the-Art

U.S. Department of Health and Human Services
Public Health Service
Agency for Health Care Policy and Research

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Mary L. Grady, Editor

U.S. Department of Health and Human Services
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Foreword

The Agency for Health Care Policy and Research (AHCPR) convened this conference to provide a neutral forum for discussions about the designation of innovative medical technologies as experimental or state-of-the-art. Presentations were from diverse viewpoints, and speakers included policymakers, practitioners, manufacturers, legislators, payers, attorneys, ethicists, and others involved in decisions about health care technology designations.

These proceedings offer insight into the ongoing debate that surrounds new health care technologies and decisions about their effectiveness, availability, and use.

We hope that this volume will serve as both a foundation and a springboard for expanded dialogue among all those concerned about development and use of new health care technologies. AHCPR invites you to participate in this dialogue and welcomes your comments.

J. Jarrett Clinton, M.D., M.P.H.
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Preface

This volume features the presentations and discussion from the conference, "New Medical Technologies: Experimental or State-of-the-Art?" convened and sponsored by the Agency for Health Care Policy and Research. A panel of experts provided their perspectives on the critical issues that affect determinations about when and if an experimental endeavor has moved to that level of care believed to represent the most advanced and proven intervention available.

These issues concern the entire spectrum of the medical community and the public as well. Thus far, the medical community has paid inadequate attention to this problem. Indeed the approach taken by those involved in decisions about health technologies has dramatically increased the divisive and fractious nature of this debate as evidenced by an increasingly frequent resort to the legal system to settle the point. Few would disagree with the proposition that to date the medical community has failed to provide sufficient clarity to this issue.

In December of 1862, Abraham Lincoln sent a message to Congress. He said, "The dogmas of the quiet past are inadequate to the stormy present." And he said, "The occasion is piled high with difficulty and we must rise to the occasion. As our case is new, we must think anew and act anew."

AHCPR has taken a first step by providing an opportunity for interested parties to make their perspectives clear on this issue and begin a process of thinking anew to the benefit of the public health of the country.

Thomas V. Holohan, M.D.
Director
Office of Health Technology Assessment
Agency for Health Care Policy and Research

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Ethical Perspective

Thomas V. Holohan, M.D.

Dr. Edmund Howe, our scheduled speaker on ethics, is unable to be here, so I will speak from the ethical perspective. Although I am not a specialist in this area, I have taught an ethics course at the Uniformed Services University of the Health Sciences Medical School for the past 4 years.

Dr. Howe's abstract addressed the conflict between a paternalistic view of medical care and the principle of patient autonomy. He correctly pointed out that society's current consensus tends to favor autonomy in choosing those diagnostic or therapeutic options that may be offered.

I will not present what I can only presume to be Dr. Howe's thesis, instead I would like to raise a series of questions about ethical considerations that are relevant to the provision of novel or innovative care. My hope is that by considering these questions, we can determine the ethical framework within which treatment decisions must be made.

First, we must remember that, broadly speaking, ethics has virtually always been an integral part of the practice of medicine. Dr. Erich Loewy in a paper on teaching ethics to medical students pointed out that ancient texts on medicine abound with references to the role of ethics in determining permissible actions. According to Plato, the difference between art and craft is that art has a moral end, and in a craft, the end is the technical activity itself. Traditionally, medicine has been considered an art that has a moral end inseparable from its technical activity.

In addition, an ethical or ethically permissible act is in accord with some moral standard or code of conduct. Such codes have commonly been adopted in medicine and in other professions as well. We must, however, at the same time acknowledge that individuals perceive moral dimensions differently, and the ethical environment is made up of many shades of gray. This does not mean that all moral judgments are matters of personal opinion, each as valid as the other. To posit that belief would be to say in effect that, in a given situation, all possible actions have equal moral standing—all are as good as the others. Few of us would agree with that statement.

These considerations are unsettling to those who would prefer absolute answers, but they are central to ethics which requires only relative certainty, sometimes referred to as moral certainty. For example, Dr. Dennis Doherty of Marquette University pointed out that a miracle cure is always a possibility. In fact, there is not absolute certainty that one will not occur. However, to continue to treat a patient aggressively as though a miracle was probable would in the common estimation be unreasonable. Hence, it is ethically permissible to decide to discontinue treatment because of the relative certainty that no miracle will occur. As in most decisions made in life, probability or relative certainty suffices in ethical considerations. An ethically permissible action then is one based on considered judgment or an educated opinion that may be only as good as the evidence on which it is based.

Proceeding then, I will begin with a set of questions we all need to consider: As a society, do we believe that all persons have the right of access to medical care? If that is our belief, is this right limited in any way, and if so, how? How far should the principle of autonomy extend? On the assumption that there is at least tacit agreement that medical care is not simply a commodity available to those with sufficient resources, we must then provide a system that will justly distribute the risks, benefits, and burdens attendant to such care.

For example, few would argue that a given patient has an ethical right to all of the particular resources of a hospital (for instance, blood products), if the exercise of that right would deprive others of their own access to that resource or service. Although this example is relatively straightforward, it is much less clear as to how far one individual's right to health care may infringe on others' access if the cost is measured instead in terms of available resources such as hospital beds, clinician services, or even financial support. Some societies have made

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Dr. Holohan, Conference Moderator, is Director, Office of Health Technology Assessment, Agency for Health Care Policy and Research.

such choices explicit, such as the British National Health Service.

How does this concern relate to new technology? In the case of emerging technology, the issue is further clouded by concerns about whether the service is undeniably beneficial to the patient. One could argue that a right to medical care does not ipso facto imply a right to all care. Benjamin Freedman of the McGill Center for Medicine, Ethics, and Law pointed out that although patients are ethically entitled to treatment, the term "medical treatment" must be defined by medical and scientific data, and a right to treatment does not encompass every intervention.

Is there then an ethical right of access to an innovation prior to its having been demonstrated to provide a therapeutic advantage? Dr. Mathilde Krim has advocated the provision of unproven drugs to treat patients whose lives are in jeopardy, not out of a wish that the treatment will work, but out of respect for a patient's right to fight for life with any tool.

In considering the treatment options for seriously ill newborns, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research allowed the provision of what it termed "futile treatments" if they were done in accordance with parental preference. In this case, the concept of autonomy was believed to be paramount. What would be the ethically permissible decision, however, if the provision of futile care was demonstrated to deprive other patients of resources appropriate to their care?

The issues regarding innovative technology become even more complex at the bedside. A physician's first ethical responsibility is to his or her own patients' welfare, and that responsibility, in general, transcends those to society at large. We have not yet charged the individual physician with the overt preservation of resources to the detriment of his particular patient. In addition, most patients believe that their doctor will do all he or she deems necessary in their best interest.

The ethical problem for the physician who provides an innovative aspect of medical care is particularly intense. One view has held that in the case of an illness for which there is no effective treatment, if a physician knows of even one case in which a patient responded, the clinician could recommend that treatment. Before an intervention has reached acceptable levels of scientific certainty, however, there is no proof of effectiveness, and to offer therapy as though such proof exists is misleading. Moreover, clinicians' recommendations may be subject to enthusiasm for or belief in an intervention in the absence of reasonable evidence for benefit.

On the darker side, the advocacy of an intervention may be related to the financial benefit of the practitioner. In the latter instance, the ethical implications of such behavior need no further elaboration.

Patients by their very nature are among the most vulnerable persons in society. A greater or lesser degree of coercion may exist in the patient/physician relationship, and patients may feel compelled to agree to certain forms of care to maintain their access to treatment or the desired relationship with the caregiver. Such circumstances require careful, precise judgment on the part of the clinician. Enthusiasm for innovation is no substitute for respect for persons or the principle of beneficence, that is, doing good and avoiding harm and observing the principles of distributive justice.

Some years ago, a baboon's heart was transplanted into an infant at a West Coast medical center. Was this procedure performed because it had been concluded that it was inherently reasonable, the expected benefits outweighed the risks, and relevant ethical principles had been met? In that same time period, a surgeon in the Southwest implanted an artificial heart in a patient even though the Food and Drug Administration had expressly forbade any further implantation of such devices based on the results of several prior studies. The surgeon's response was that the circumstances represented an emergency, there was no alternative, and he would do it again. Does this treatment constitute an ethically permissible act? Perhaps more importantly, was that question ever raised? Is it ethical to proceed in the presence of data indicating that the treatment is not effective? Further, should either of these extreme cases be evaluated in terms of the resources required? Finally, how much weight need be given to the patient's desire for the treatment?

We have recently seen examples of well-respected clinicians who have stated and testified in court that a particular innovative treatment was the best available therapy for patients with a life-threatening disease. Several written statements to that effect have from time to time been forwarded to me. Yet, a meeting of experts in the field convened by the National Institutes of Health concluded that the benefit of the procedure had not been adequately demonstrated and that a randomized trial was necessary to determine the most effective approach. Some of the clinicians who had advocated the technology as the best available treatment are participating in this trial, wherein patients are informed in writing that it is not known to be superior to standard therapy and therefore random assignment to treatment groups is considered to be ethically permissible. On which side of this question do we believe the ethical imperative lies? In the practice of medicine, the advocacy of a novel procedure occurs frequently on the basis of personal interpretation of evidence or expert opinion, but at the same time others have suspended judgment while awaiting evidence that would permit more definitive assessment of probable benefit. Here again, should the question of resource demands be a consideration?

Finally, these questions increasingly have been referred to the courts for determination. Although the legal perspective will be provided by Mr. Stein, I should not fail to point out that law and ethics are not identical. That is, although a final decision as to how one must act may be that of the court, courts issue legal and not ethical pronouncements. One ethicist has said, "As law would balance interests, so ethics balances values."

One can clearly posit circumstances in which an individual or an institution may act unethically but not illegally. Conversely, the civil rights movement has provided many recent examples of decisions to act illegally in service to an overriding ethical imperative.

If in this brief discussion I have raised more questions in your minds than I have provided answers, I must admit to satisfaction, since I believe the very essence of ethics is in the question, not in the axiom. On a personal note, in my own career in medicine, I have noted the virtual absence of formal training in medical ethics until recent years. Such decisions were generally made on a case-by-case basis, grounded in the often poorly thought-out proclivities or even idiosyncracies of individual practitioners. Dr. Edward Pellegrino, head of the Bioethics Institute at Georgetown, lectures each year to the students at the Uniformed Services University of the Health Sciences School of Medicine. He has told the medical students to remember that a patient's best protection is ultimately the doctor's own character and ethical principles. That concept is perhaps nowhere as crucial as in the provision of innovative care or emerging technologies to our patients.

Legal Perspective

Robert E. Stein, LL.B.

My remarks at this conference are being made principally in my capacity as a member of the American Bar Association's (ABA's) Coordinating Committee on AIDS (acquired immunodeficiency syndrome), although I am also an attorney in Washington, DC, and an adjunct professor at Georgetown University where I teach a seminar on human immunodeficiency virus (HIV) law, policy, and dispute resolution. It is not often that a group of physicians and health policy experts willingly requests the comments of a member of the legal profession, and for that reason, as well as because of the ABA's and my own interest in the subject, I am happy to participate in this conference.

It is sometimes said, and not always jokingly, that if two lawyers get in a room together, there is going to be an argument. For that reason, the ABA's accomplishment—with over 350,000 members—through its governing body, the House of Delegates, in reaching agreement on a very succinct set of policy recommendations dealing with AIDS should not be underestimated. It is certainly true that in this area, as in so many others in which there are divergent interests and the law is involved, there can be significant differences of opinion. The achievement of the ABA, therefore, in agreeing on a set of clear and well-thought-through recommendations is to be applauded.

The specific reason for this conference is to reflect on the differentiation between experimental and state-of-the-art medical technologies. There really cannot be a resolution of the outstanding issues, and this conference is not going to resolve them, but the breadth of the perspectives of the individuals and groups attending the conference will give the Agency for Health Care Policy and Research (AHCPR) better tools to help find workable solutions to some of the questions.

From the perspective of the ABA recommendations, these issues have been addressed in the context of drug development for HIV and, I should add, for other life-threatening diseases. In this sense, HIV is seen by some as a paradigm for many serious illnesses and conditions. For others, HIV is viewed as unique and an exception to what the process is or should be, since they consider that the process is working pretty well at the present time. Which of these viewpoints is adopted in the future will determine some of the answers to the questions before us.

The portion of the ABA recommendations dealing with drug development for HIV falls into three different categories. First, issues surrounding the acceleration of the approval process; second, strengthening and expanding the ways in which drugs and other therapies can be made available to a broader group of individuals prior to full Food and Drug Administration (FDA) approval; and third, issues relating to the cost of experimental drugs and reimbursement questions about who pays for the drugs and attendant medical care.

Each of these issues has an impact on the ways in which innovative medical technology—including drugs, vaccines, and devices—are used and also, in the case of HIV, has a very direct bearing on whether the technology is considered to be experimental or state-of-the-art. These are not three discrete areas; each interacts with the other. Consequently, there has been a blurring of the distinctions between experimental and state-of-the-art therapies because of the special nature of HIV and other life-threatening diseases.

In a discussion of the changes brought about by AIDS or believed to be needed, it makes sense to start with the baseline. The FDA is charged by the Food, Drug, and Cosmetic Act with reviewing products, drugs, vaccines, and biologics and approving them for distribution when they have been shown to be safe and effective for particular indications.

Traditionally, this has been done through structured clinical trials in which efficacy is demonstrated by comparison with a placebo. There are good reasons for the processes, as there is a definite consumer interest in the role that is played by the agency—a role on which other Americans and certainly people outside the United States have come to rely.

Mr. Stein is member of the law firm of Blicker Futterman & Stein and a member of the American Bar Association's Coordinating Committee on AIDS.

Given the exigencies of HIV that the virus is fatal over time, that there is no cure, and that, for an increasing number of people with HIV, experimental drugs provide their only hope and their only access to medical care, many have come to believe that there should be ways to make promising agents available more quickly and to a larger group of people. Thus, in one of its first recommendations, the ABA urged that the FDA continue and expand efforts to accelerate, review, approve, and disseminate HIV-related drugs, vaccines, and medical devices. It was recognized even before the Lasagna Committee and the Edwards Commission that the approval process—especially where it pertains to serious and life-threatening illnesses such as AIDS—deserves the full attention of the FDA and that if additional personnel are needed in order to meet these needs, the FDA should get the increased personnel necessary to expedite FDA review. The FDA has made a number of efforts in that direction.

Once a drug has been demonstrated as safe and there is preliminary evidence of efficacy under the regulatory system—and, at least in my opinion, the legal system certainly includes the regulatory system in addition to decisions that are rendered by courts—there are still several steps to go to develop a better understanding of efficacy. What may appear to be experimental to some, may seem to be state-of-the art to individuals without viable alternatives; they want to take part. Moreover, for a number of people, clinical trials can be difficult to get into because once a trial is fully subscribed, it may not be available.

Therefore, the ABA in its recommendations supported community-based drug trials as a way to make experimental therapies available to a wider range of individuals with HIV. The recommendations do, moreover, make clear that the FDA should continue to require demonstration of drug efficacy in well-controlled studies. The particular conflict has not turned out to be as serious as originally thought. The expanded-access program for dideoxyinosine, for example, which was recently approved by FDA, confirmed that clinical trials can proceed, even though it takes a little longer to fill them up while the drug is being made available through an expanded-access program to many thousands of individuals for whom there is no other available therapy.

Another related development which is also confirmatory of the blurring of lines is that the trial for a better drug will give volunteers an existing state-of-the-art drug as a control rather than a placebo. This was done, for example, in the recently concluded study that compared an experimental drug, Foscarnet, with an approved therapy, Ganciclovir, for cytomegalovirus retinitis. Both drugs are used for that purpose, and Foscarnet was recently approved. It is considered by many to be unethical to give a placebo to a person with a terminal illness when the purposes of the trial will be just as well served by comparing the new candidate with an approved drug.

There is a danger, though. Some of you may have seen the article in the *New York Times* about buyer's clubs, and there is a fear that if some people in a clinical trial are getting either a placebo or the control drug, they still may seek an experimental drug through an underground market. Personally, I do not think that is a good way to conduct a clinical trial, and it is certainly not going to give the needed results, although from the perspective of the individual, it is understandable.

In 1989, when the ABA recommendations were approved by the House of Delegates, the concept of a treatment investigational new drug (IND) was supported as a way of making experimental drugs more widely available to patients with serious or life-threatening diseases when there is no satisfactory therapy. Since then and in addition to treatment IND, a number of concepts, including emergency INDs, compassionate use, open-label protocols, and the expanded-access program, have all included ways to provide drugs to individuals or groups before they are approved.

There is also a proposal for a parallel track mechanism. There is conditional approval and most recently early approval with postapproval studies—the phrase in use is "postmarketing studies," but it is after the approval process that we are really talking about. These concepts are important and should be critically examined, and at least one should be approved. There are good reasons to make certain drugs available to as many people as possible, as long as the clinical trials are proceeding and the FDA is able to continue to collect data, even if it is after the approval of the drug.

The timing of when a drug ceases to be viewed as experimental and becomes state-of-the-art so that it can be prescribed by a physician continues to be blurred. The official sanction of an institution such as the FDA is very important to the determination. Expansion should be viewed not only in terms of the number of people but also the groups of people who have access to the drug. Minorities, elderly persons, women, and children are often excluded from clinical trials, but certainly they should be considered in expanded-access protocols so long as appropriate informed consent is used.

This brings us to the third and sometimes most difficult and controversial part of the discussion: the critical question of reimbursement or who pays for these therapies. Until recently, this was one of the few bright lines that could be pointed to in determining the experimental nature of a drug. With only a few exceptions, the costs of clinical trials are borne by the drug companies. If there is an expanded-access program, the cost to the company of the drug alone can be significant. In addition, there are the costs of attendant medical care, including ancillary treatment, testing, reporting, and recordkeeping. It is not clear who is to pay for that.

Both public and private insurers have looked to the FDA's blessing—new drug approval—as a condition of payment. Moreover, although a physician can prescribe an approved drug for a patient for whatever reasons the physician believes appropriate, many third-party payers will only reimburse for those indications for which the drug is approved. For example, a drug such as azidothymidine (AZT) was viewed as approved or state-of-the-art for some people and some purposes and still experimental and therefore not reimbursable for others. The ABA recommendations indicate that insurers should be encouraged to include coverage of drugs that have been approved by the FDA under a treatment IND mechanism or approved generally—which would include some of the expanded-access categories—for whatever indications the responsible physician believes to be appropriate.

A number of court decisions have held that, where there are good medical reasons to use an experimental therapy—for example, bone marrow transplant for a person with HIV or breast cancer—the fact that the bone marrow transplant is investigational or experimental does not bar reimbursement so long as the procedure is not specifically excluded in the plan contract. In one New York State decision, Empire Blue Cross and Blue Shield was ordered to pay for a bone marrow transplant procedure for a person with AIDS because it was believed that the use of the transplant had been validated in other areas and could be helpful in his case (*Bradley v. Empire Blue Cross and Blue Shield* 562 NYS 2d 908, 1990).

In other cases involving autologous bone marrow transplant for breast cancer, the courts have gone in both directions. Federal courts have held that a plan exclusion was arbitrary and capricious if it did not exclude the therapy specifically. The court ruled that the criterion should be whether the procedure was generally accepted medical practice by oncologists in the area at the time the claim was denied. This would mean, therefore, that for individuals with serious illnesses for whom there are no available alternatives, drugs or procedures that are in some way considered state-of-the-art by the courts according to some decisions should be covered by the payers, both for the specific indications for which they are approved or for other off-label uses for which the treating physician believes they are appropriate.

The courts have said that they will defer to recent medical opinions when such opinions are available. One of the difficulties of the advocacy system, however, is that it pits one medical expert against another medical expert, and it is very difficult for a judge to reach a decision. When that happens, more often than not, finding for an individual who is in need may seem to be the appropriate and compassionate, if not necessarily always the correct, way to go.

The American Bar Association has made it clear that it is not concerned solely about drugs paid for by private insurers; the ABA also contends that the Secretary of the Department of Health and Human Services should require all State Medicaid programs to reimburse for HIV-related drugs that have been approved by the FDA. I note that it took almost 2 years after AZT was approved before all States would pay for its use.

Given the high costs of new therapies for HIV disease and the reliance on insurance for payment, disallowing reimbursement is the equivalent in some cases of denying treatment. Thus, the bright line dims here too as the urgency of dealing with AIDS and other serious illnesses has been instrumental in rewriting the rules for reimbursement.

The Keystone Center in Colorado has convened a group to examine issues relating to expanded access to drugs and biologics for AIDS and other life-threatening illnesses. The group includes individuals from Government, the insurance community, pharmaceutical companies, investigators, activist organizations, and researchers. The group will seek to reach a consensus, hopefully over the next year, on the ways in which these various issues and constituencies interact.

A topic not covered within the ABA framework is the development of HIV vaccines. Concerns with liability both during the clinical trial or experimental phase as well as concerns once a vaccine is approved are certainly contributing factors to a company's willingness to develop an HIV vaccine. Therefore, it is important that mechanisms be developed to anticipate these issues, much in the way they have under the National Childhood Vaccine Act for vaccines for childhood diseases. It is recognized that we have much less experience with an HIV vaccine, but during the early stages of vaccine development, there have been discussions about these issues between the Government—principally the National Institutes of Health (NIH)—and manufacturers; in addition, these concerns have been the subject of legislation in two States, California and Connecticut, which take differing approaches to dealing with the issues.

Vaccines are different from drugs; in the early stages of vaccine development when safety and immunogenicity are being sought, the volunteer must be made to understand that no benefit can be expected. Therefore, to get the vaccine to move from experimental to state-of-the-art, it is necessary to reassure companies that liability concerns will not overwhelm them while at the same time reassuring potential volunteers that they will be compensated for any injuries that are attributable to the vaccine. Even when a vaccine is approved, methods and standards must be sought to assure a supply of vaccines and to find ways to compensate injured individuals.

The HIV vaccines involve other important legal issues; for example, during clinical trials if a vaccine is found to be effective—meaning that an antigenic reaction is present—an individual will develop antibodies. Should that individual seek an HIV test as a result of a blood donation, search for a particular job with the military or foreign service, or want to get an individual health or life insurance policy, the presence of antibodies might result in a negative determination.

For this reason, NIH has launched a program whereby individuals involved in clinical trials will be given documentation by the Federal Bureau of Investigation indicating that they are participating in a clinical trial, and an 800 number has been set up to provide information on the kind of vaccine taken by the individual. It is possible as a result of the Western Blot Test to distinguish between viral-induced antibodies and those induced by the vaccine, at least for the envelope vaccines currently under investigation. Thus, this process can reduce the concerns of some volunteers as to the adverse effects of participating in a trial and make it easier for vaccine development to proceed.

Additionally, NIH has sought to inform all insurers of the potential problems with Western Blot interpretation, and all have agreed that should a person provide documentation, they will take a closer look at the antibodies to determine whether they are viral or vaccine induced. Moreover, some insurers have agreed that where an injury is not expected, coverage will be provided. This is interesting because normally, as we have been discussing, insurers do not reimburse for experimental therapies or for the unintended results that may flow from taking an experimental therapy.

This is a departure from the traditional reimbursement strategy, one which has been brought about by the exigencies of the HIV epidemic. How it is extendable to other situations remains to be seen. This mixing of state-of-the-art diagnostics with experimental therapy may make it possible to remove some of the concerns that volunteers have had during the vaccine development process.

Finally, it is my hope that the participants at this conference will keep in mind the statement made by the historian William McNeil in his book *Plague and the People*:[1]

> Infectious diseases which antedated the emergence of human kind will last as long as humanity itself, and will surely remain, as it has been hitherto, one of the fundamental parameters and determinants of human history.

One infectious disease, HIV, has already had an influence on the debate that is the subject of this conference.

The extent to which law and policy recognize these problems and work with the scientific community will be crucial to both our better understanding of these diseases and our ability to control them effectively.

Reference

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Minority Population Perspective: New Ethical Concerns in Relation to New Technology

Harold P. Freeman, M.D.

Diseases always develop under certain human circumstances which, to a large extent, can be measured and defined. In particular, diseases invariably occur in the context of definable social, physical, economic, and political conditions. If one looks only at the scientific aspects of disease and fails to take into account the human conditions within which the disease occurs, understanding is limited.

I have spent 25 years—my entire medical career—as a surgeon in Harlem, a community that is 41 percent poor and 96 percent black. Over a recent 20-year period, nearly 50 percent of women presenting with breast cancer at Harlem Hospital were incurable on admission. The crude 5-year survival for these women was 32 percent compared with 60 percent for American white women.[1] Soon after coming to Harlem, I realized that being a highly trained cancer surgeon did not matter very much for many of my patients because there was no possible cure.

We have shown that over the last 20 years in Harlem there has been no change in overall mortality, whereas in the rest of nonwhite America and white America, the last several decades have seen a great decline in overall mortality. The question arises as to what is unique about a community such as Harlem—what prevents mortality from declining. (No doubt there are similar communities interspersed throughout America which comprise poor people of all races and cultures.) The causes of death in Harlem in order are cardiovascular disease, cancer, cirrhosis of the liver, and homicide. Note that the first two causes are similar to the rest of America. In a rather dramatic comparison, we showed that a black male growing up in Harlem has less chance of reaching age 65 than does a male growing up in the third-world country of Bangladesh.[2] This is a very disturbing example of the magnitude of disparities in survival among various communities within America. The implication is that, with respect to survival, Harlem is a third-world community within the so-called first world. This finding raises deep ethical and moral questions concerning the application of our great technological advances.

The Swedish economist Gunnar Myrdal came to this country some 50 years ago and studied the American socioeconomic system. Looking objectively from his point of view as an outsider, with very few assistants and no computers, he made some assessments in 1944 that proved to be accurate and had profound implications. He predicted that significant social conflict would occur in the United States, a Nation founded on democratic principles, based on the Declaration of Independence written more than 200 years ago. Although according to that document all people are created equal, in practice this was a sham because at the time of Myrdal's analysis, a significant number of Americans, the former slaves, were neither regarded nor treated as equals. Myrdal recognized this incongruity and correctly predicted that it would result in major upheaval.

In the 1950s and 1960s, Martin Luther King, Jr., and others protested this double standard for white and black Americans and set into motion changes that resulted in the elimination of legalized segregation in America. Since then, much progress has been made, but the process is not complete. The negative socioeconomic effect of this Nation's long past history of perpetuation of legalized segregation is believed to be a key factor in explaining many of the health disparities between races that still persist.

Certainly we have made extraordinary progress over the last decades with respect to technical advances and scientific understanding. Measures of this progress are the significant breakthroughs that have recently been achieved in understanding some of the fundamental molecular processes that explain pathological changes. But today we still have an American dilemma regarding our application of scientific advances. This dilemma is seen most dramatically in America's failure to provide basic health care to all Americans irrespective of their ability to pay. Moreover, technological advance has the effect, in my opinion, of heightening disparities between those

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who have and those who have not—a very peculiar paradox. In other words, as we advance our knowledge, the disparities between the poor and those who are middle class and affluent are placed in greater contrast.

For a better understanding of these issues, it is important to define the meanings of race and economic status with respect to the incidence and outcome of disease.

Race in Relation to Disease

Race may be seen in relation to its historical, cultural, and genetic meanings, any or all of which may have significant implications. The history of a given racial group can be a powerful determinant of the current socioeconomic status of that group. As a dramatic example, consider the fact that, historically, black Americans have been legally free in this country for only 25 years, having before that experienced 250 years of slavery and 100 years of legalized segregation. The negative socioeconomic effect of this Nation's long history of legalized segregation and slavery is believed to be a key factor in explaining many of the health disparities between races that still persist.

Viewed from another perspective, race may be seen as a gross variable for culture. If, for example, a population designated by race has common ancestors, similar social and physical environment, and a shared communication system, its members will tend to have a similar tradition, value system, belief system, and world view. These shared elements lead to common lifestyles, attitudes, and behaviors. Such cultural factors deeply influence health status, and any successful intervention must necessarily take these powerful cultural realities into account.

To date, there is no known genetic basis to explain the major differences in disease incidence and outcome between races.

Poverty in Relation to Disease

Poverty, in contrast, is associated with low educational level, substandard living conditions, an inadequate social-support network, unemployment, poor nutrition, risk-promoting lifestyles, and diminished access to health care. Diminished access is often manifested by low quality and inadequate continuity of health care, as well as insufficient access to methods of disease detection, diagnosis, treatment, and rehabilitation. Moreover, poor people tend to concentrate on day-to-day survival, often develop a sense of hopelessness and powerlessness, and may become socially isolated. Poor Americans have an overall higher mortality and in general do not enjoy the same health status as those in the mainstream of American society. For example, poor Americans have an increased incidence of cancer and 5-year survival rates 10-15 percent lower than those for other Americans. Cancer is the Nation's second leading cause of death.

Interrelationships of Race, Poverty, and Disease

Although neither race nor poverty is an absolute indicator of disease incidence and survival rates, each is a surrogate of predictable conditions and circumstances. Setting aside historical considerations, the significance of race with respect to disease is generally limited to race as an indicator of a specific culture and lifestyle. We conclude, however, that economic status, irrespective of race, prevails as a more powerful surrogate of human conditions and circumstances.

We theorize that poverty acts through the prism of culture—a factor that can either diminish or accentuate poverty's negative effects. For example, poor people belonging to a culture whose members do not smoke, do not drink alcoholic beverages, and have a low-fat, high-fiber diet will have diminished risk factors compared with those in a culture whose members smoke and drink heavily and consume a high-fat, low-fiber diet. On the other hand, regardless of culture, poor people have diminished access to health care (Figure).[3]

Poverty in America

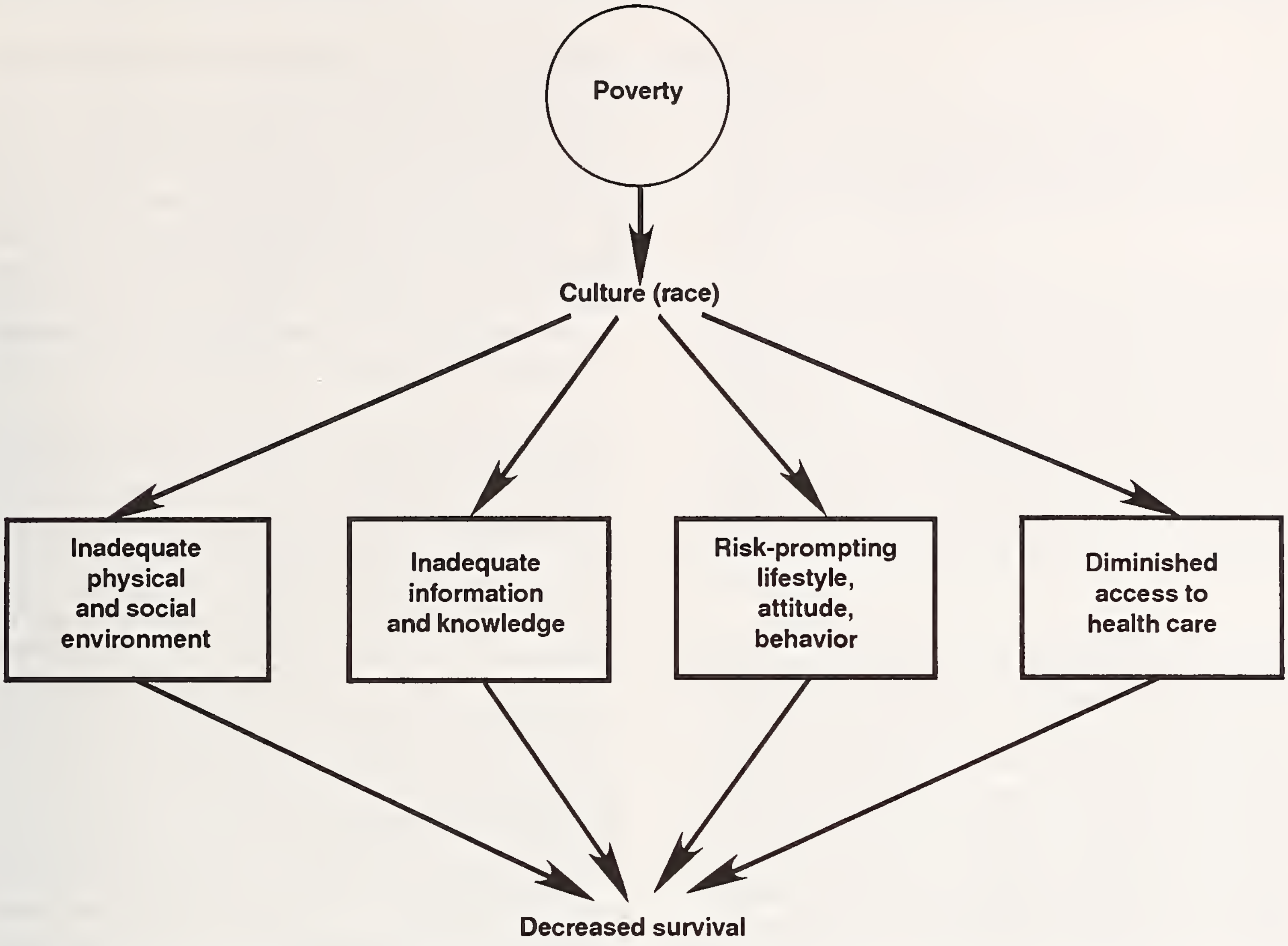
An estimated 34 million Americans are poor by the national standard of poverty (about $13,000 per year for a family of four). Two-thirds of the poor are white, but only 12 percent of white Americans are poor. In contrast, one-third of the poor are black and one-third of black Americans are poor. We suggest that the disproportionate disease burden shared by black Americans is, for the most part, an indication of the health consequences that befall a racial group representing one-third of the poor, one-fourth of the unemployed, but little more than one-tenth of the population.[4]

We can be proud that America has achieved a remarkably high level of medical technology and is on the cutting edge in medical research, but it is sobering to note that a significant segment of Americans have not benefitted substantially from this progress. There are over 37 million uninsured Americans who have limited access to medical care. Moreover, one out of four Americans is either poor, uninsured, or both.

Conclusions

In the past, experimental medical and surgical treatments often were tested on certain disadvantaged groups of the population, especially minorities. As a very dramatic example, note that several decades ago in Tuskegee, Alabama, in order to document the natural

Figure. The interrelationships of race, poverty, and disease; poverty acts through the prism of culture (race)


Poverty
Culture (race)
Inadequate physical and social environment
Inadequate information and knowledge
Risk-prompting lifestyle, attitude, behavior
Diminished access to health care
Decreased survival

Source: Reprinted from Cancer 64 (suppl): 324-334, 1989. Used with permission.

history of untreated syphilis, U.S. health officials withheld treatment from a large number of black males with syphilis.

The Nation's past history of at times placing certain citizens at severe risk in research designed to advance knowledge has created a degree of distrust of the establishment in such people with respect to these issues. We also observe that treatments that become state-of-the-art are sometimes unavailable to those who may have participated in proving their effectiveness. Moreover, paradoxically, technological advances tend to heighten the disparity between poor people and others.

It is important to take into account not only the differentiation between what is experimental versus state-of-the-art, but also the fundamental point that there are segments of the population who seldom receive state-of-the-art health care. For them, access to the latest experimental advances is almost never attainable.

These thoughts suggest that as a Nation our technology has advanced to a higher level than our humanity. Fundamental solutions must begin with justice in the distribution of medical resources. Policymakers should reflect deeply on these moral and ethical issues as they proceed with future planning.

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Discussion/Questions and Answers - Session 1

Q: [Dr. Holohan] How can we best address the ethical concerns of distributive justice and equity in terms of appropriate sharing of both the burdens and the benefits of technology? As Dr. Freeman has pointed out, the question of whether private insurance will cover a treatment that is on the bubble or assumed to be experimental is not relevant for millions of Americans who are poor or uninsured.

A: [Mr. Stein] It is difficult to address that question without looking at the entire issue of how health care is provided in this country. At the same time, it is also difficult to deal with a specific problem if what you are considering is something that, although desirable, is clearly not going to be achieved in the near future.

First, a conscious effort should be made to provide therapy during a clinical trial phase or an expanded access phase—where there are individuals in need—to as many people as possible. Certainly when dealing with human immunodeficiency virus (HIV) and other serious illnesses, it makes sense to do so. Second, a much more conscious effort must be made in the future to expand clinical trials to individuals who normally do not participate in such trials. Third, if the only medical care some individuals receive is in clinical trials, ways should be found to provide additional basic care to those individuals.

A: [Dr. Freeman] We are talking about sophisticated advances in technology and the ability to treat, of which only a part of America benefits. There are 34 to 37 million uninsured persons, for example; these people do not have access to even so-called basic health care. It is a heroic leap to consider whether they would receive technologically advanced therapies.

Thus, I am dealing on the ground floor where I work. I am dealing with people who are not even in the running for some of the things that we are talking about. It is an American problem, not a problem associated with a particular community. All around the country, people who are white, Hispanic, black, American Indian, and others are in this bind, and none of us is completely out of it. I do not know how many people at this conference could miss next month's paycheck without falling into this circle where they might have an access problem.

So, I would like to remind us, and hopefully the report from this conference will stress the point, that there are some fundamental things that have to be done while keeping up the pressure for advances. Advances are important, and I am not speaking against them. Rather, some balance is needed to bring basic services to segments of the population that have no access to these services.

A: [Dr. Holohan] In other words, while not minimizing the importance of technological development and discussions of when it is considered standard care, both standard care and available new technology prior to the decision that it is standard, by whoever makes that determination, have to be provided on a broad scale. Discussion or debate about whether private insurance, for example, would cover a therapy that was experimental versus state-of-the-art is irrelevant to a significant fraction of the population.

Q: [Mr. Stein] In terms of life-threatening conditions, how should we give more weight to autonomy than has been given? Further, if you give more weight to it, does that mean whatever flows from that decision, including access to therapies whether proven or not and reimbursement for those therapies, is different for life-threatening conditions than for other kinds of conditions? An example would be the discussions over breast implants which make a distinction between individuals who have had mastectomies and those who want an implant for cosmetic reasons.

A: [Dr Holohan] There appears to be a growing belief that autonomy should clearly ascend over what traditionally in the United States has been a rather paternalistic medical care system. That is probably generally agreed to be to the good. My questions are related to how the emphasis on autonomy has to be mitigated by the concept of distributive justice and equity. I think that alludes to some extent to the point that Dr. Freeman was making. In a sense, it is an interesting discussion because I mentioned both autonomy and equity in distributive justice; Mr. Stein's discussion was oriented more toward autonomy and Dr. Freeman's more toward distributive justice. There clearly has to be a balance.

In terms of the severity of the disease, that is probably not a major issue at present. Most of society probably believes that more allowances must be made in circumstances where the disease is serious or life threatening. As Mr. Stein alluded, the Federal Government has done that; the FDA has done that. Certainly the National Institutes of Health has utilized a comparable approach for some time.

Q: [Helen Philliou, Reinsurance Company] Our company provides coverage for self-insured employers under the Employee Retirement Income Security Act (ERISA) plans. I would suggest that cost is a relevant aspect for you to consider because the balloon is growing; there is a pushing down at one end and a bulging at the other end. I see on a daily basis bills for care that is considered state-of-the-art or questionable experimental but costs more than $10,000 per day. My point is if employers who are paying into this self-insured plan saw some relief in the rate of escalation of the inflation, they might be more willing to listen to a national plan that offers health care for everybody.

I am a nurse by background, and I have a nurturing sense. I find it very difficult to accept that there are many people in this country who do not have health care. But the cost is prohibitive. You see premature infants on a heart/lung bypass machine now. The cost of that is $11,000 per day. These children reach the maximum on their benefits within a year sometimes, if they live. Something must be done to address cost as a factor, even though it is a dirty word in the medical community. The fact is that it is going to break the system.

A: [Dr. Freeman] I agree with that; cost is a factor. The reality, though, is that when people get sick—very sick—it does not matter whether they are insured or not. They will get into the hospitals, and they will be treated, and it will cost a lot of money. In fact, it will cost more because they come in late. The money is going to be paid. The country must decide when it is going to pay for the treatment, early or late. Take cancer, which is my field. If you have cancer and you wait 2 years to come in with advanced cancer, it does not matter whether you are poor or whether you have insurance, you are going to get into the hospital to die, and it is going to cost a lot of money. Studies have shown how much more it costs to treat late cancer compared with preventing and diagnosing it earlier.

So, I agree with your point about cost, but I do not believe we are saving money. We may save money during a certain Congressman's 2 years in the Congress. The problems that we are facing with respect to health care are long-term problems in terms of solution. The people who are making the decisions are trying to make decisions on annual budgets or 2-year budgets, and it is not possible to do that. It becomes an ethical and moral problem for America. The problem goes beyond the insurance business. It is the business of America to protect its citizens, and we need justice in the distribution of medical resources. We will pay the price, either early or late.

A: [Mr. Stein] I agree with what Dr. Freeman has said. What we are doing, it seems, is trying to deal with this problem in several different ways. One could look at the Oregon approach in which they say that there are some things they are going to cover and some things they are not, even on a Statewide basis; for example, eliminating certain therapies above a certain age. This is also being done with ERISA where an employer under a plan has an option to say "we are going to continue to cover certain kinds of therapies or not cover certain kinds of therapies or not cover certain diseases," and there are some recent cases—which are being challenged—in which an employer cut from $1 million to $5,000 coverage for HIV, when the company knew that it had an HIV-infected employee on its payroll. A number of groups have filed a friend-of-the-court brief saying that under ERISA this does not make sense.

To return to something I said in my previous comments, we need to look at our overall health system. We need to look at it very carefully. Only when we do that will we be able to get some of the answers to your questions.

Q: [Denman Scott, American College of Physicians] Is it ethical to exclude some experiments, for example, a trial of the baboon heart as you mentioned, from the research agenda or from sources of public funding, and should we have a debate in the Nation on the shape of the research agenda rather than defining it on a disease by disease, technology by technology, ad hoc basis?

A: [Dr. Holohan] To the question as phrased, I would answer yes; there are experiments that could be deferred solely on an ethical basis. I am not going to argue that there would necessarily be a consensus on what those experiments should be, but most ethicists with whom I have had contact and about whom I have read would argue that, yes, there are certain experiments that should be deferred—perhaps not necessarily the implantation of a baboon heart in a human infant, although that is a rather dramatic example.

The other question pertains to evaluating the research agenda in toto. Is that an appropriate way to look at the research agenda in health care, instead of a piecemeal ad hoc approach on an item-by-item or technology-by-technology view? I think the panelists could initiate a response to that.

A: [Dr. Freeman] The question is a very pertinent one. We declared a war against cancer 20 years ago under President Nixon, and the war has been fought rather well on the research front. What we are seeing now, though, is that research has not been translated to help the public in general in an even way and that we have a deficit of the research that would transfer technology to serve the public. It is a difficult point to say that we should limit scientists from research because some of the greatest ideas we have come up with looked pretty ridiculous at the time people began to study them. They came up with something extraordinarily important, however.

So, although I would hate to say that we should limit that kind of research, on the other hand, I believe we should target research in a comprehensive way—research that would help us to transfer knowledge to the American public. Two important points are to continue our attempts to understand the basic biology of life through research and, at the same time at every step of the way, to transfer what we know to the American public in a broad sense.

I do not think the second part has been well satisfied. We have not conducted research that has to do with the transfer of technology. Some of the answers that have to be found are soft answers, but we only do hard science for the most part. The answers are soft, and the science, like anthropology and other sciences that we need to know more about to translate technology to people, is being deemphasized.

Q: [Steven Sieverts, Blue Cross/Blue Shield of the National Capital Area] I want to go back to this concept of autonomy that Mr. Stein and Dr. Holohan mentioned. I suspect that if one did a LEXIS search of the word autonomy in the bioethical literature, one would discover that 9 times out of 10 or perhaps more often than that, it deals with the emerging rights of patients to refuse care and, to some extent, the right of the patient to choose from offered alternatives for care.

The new notion, which seems to be surfacing in the last couple of years and of which we heard more about in Dr. Howe's abstract, is that autonomy means the right to demand and get care even if medical science believes it not to be efficacious and effective care. That is a rather startling turnaround of a concept, it seems to me, particularly when we have made an imperfectly executed societal decision that medical care costs should be shared in the medical commons—that is, we should all contribute to a pool out of which all of us can get the care we need. If the notion now arises that people can simply demand at will and get services that are medically determined not to be efficacious, where are we going? I would like to hear Mr. Stein's comments on that.

A: [Mr. Stein] Perhaps because I have not done the search, I viewed autonomy in a more simplistic way as the right to make a choice for oneself, whether it is a choice to refuse or a choice to receive. I think you are right; in the last couple of years, there have been activists dealing with HIV who have been both vocal and organized in a way that activists have not been in the past. They have argued for the right of individuals to obtain therapies as quickly as possible because their lives are at stake. This is not new in medical history, by any means, but it has just become a little bit clearer and better articulated in the era of instant media coverage.

I do not want my earlier remarks to be construed as meaning that I think this is the only criterion that should be used. I did not mean that. The question is: should it be used equally in other areas, or is this something unique and therefore it should be distinguished from everything else? I am not sure how that is going to come out, but I certainly do think that without becoming overly paternalistic, there is a very legitimate role for making a determination for society generally as to what is considered to be effective.

I will guarantee as much as one can that for those members of Congress who have been urging earlier access to therapies, the first time that there is another thalidomide, they are going to forget all of their earlier statements about "we really think you should do this earlier" and come down on the agencies that have permitted this and say "why have you done it?" So, I think the role of making a determination as to what is safe and effective is very important.

When individuals, for whatever reason, do not have any other alternatives, they may believe—and I think more weight should be given to the belief—that perhaps it is appropriate that they try something. That should be distinguished, however, from whether any time they think they should try it, somebody else should pay for it. And that is where the lines are being drawn—not whether something is considered state-of-the-art or experimental for access to it. I really think the reimbursement question is the one that we always come down to at the end, even though it is referred to at the end. I hope that I will get a little more guidance from this group in that respect.

Q: [Roger Winn, American Society of Clinical Oncology] We have come at this, in the past at least, from the opposite direction, which was coverage and the right to unorthodox or quack treatment—laetrile and so on—where we have determined that people do not have the right to that treatment because we did not feel it was in the patient's best interest.

Perhaps autonomy covers health care, which implies effectiveness and benefit rather than the right to treatment. Effectiveness, Mr. Stein, I think is the issue, as you have brought out. My question for you is, do you sense within the legal profession, since it is being dumped in your laps, any methodology for

Perspective from the National Institutes of Health

John H. Ferguson, M.D.

Virtually all of the institutes at the National Institutes of Health (NIH) are involved in research on some aspect of medical procedures or therapies that fall in the continuum from experimental to state-of-the-art. Indeed, a basic mission of the NIH is the discovery of these health technologies and the research necessary for their progress from the bench to the bedside. In that portion of the continuum where the technology is evaluated in patient populations, often with clinical trials, the attempt is made to distinguish "experimental" from "state-of-the-art" for reimbursement purposes. These decisions are generally made after the appropriate trials have been conducted.

For the purposes of this discussion, it is useful to consider four categories of medical technologies: therapeutic, diagnostic, preventive, and adjunctive. In the therapeutic category, we will consider medical and surgical divisions. In the diagnostic category, one might consider invasive and noninvasive procedures as subdivisions. In preventive technologies, we will follow the Guide to Preventive Services categories of primary, secondary, and tertiary. Primary prevention is for asymptomatic individuals—for example, routine immunization. Secondary prevention is to identify and treat those who are asymptomatic but have already developed risk factors or preclinical disease—for example, Pap smear to detect cervical dysplasia. Tertiary prevention is the application of preventive measures in symptomatic individuals—for example, insulin treatment in diabetics to prevent complications of diabetes. The adjunctive category might include various devices like hospital beds, braces, intravenous tubing, and so on.

A continuum from inception to state-of-the-art exists in all these categories and subcategories. Although the idea of the continuum is the same for all categories, the continuum itself will differ in many respects from category to category and should be approached accordingly in the decisions relating to when experimental becomes state-of-the-art for reimbursement purposes.

As a preliminary overview of the continuum for discussion, some steps will be defined employing a scheme that can be used as a straw man for modification and criticism.

- **Inception** — The safety or effectiveness of the technology is regarded by the evaluation community as untested.
- **Innovation** — The safety or effectiveness of the technology is undergoing preliminary testing.
- **Investigation** — There is insufficient evidence to determine the safety or effectiveness of the technology. Use of the technology in patient populations should be confined largely to research protocols.
- **Promising** — Given current knowledge, the safety or effectiveness of the technology is appropriate for some indications in certain patient populations.
- **Established** — The technology has been adequately evaluated for safety and effectiveness for given indications in specified patient populations.
- **Guidelines** — The technology is accepted as routine and a standard of care for given indications in specified patient populations.

Several issues require special emphasis. Once the provider is reimbursed by a large or major payer, in general, the use of a technology will spread. Therefore, it behooves those responsible for the health and safety of our citizens—public health in general—and for the use of resources to make the reimbursement decisions carefully. To spread an expensive treatment or diagnostic test among our citizens might be beneficial in the long run if the health outcomes are positive and clear. If not, we are spending precious resources for marginal or no health benefit which we can ill afford.

One should mention the "flip-side" of reimbursement for "established" technologies; that is, stopping reimbursement for a technology determined no longer to be safe or effective or to have clearly been replaced by a newer, safer, or more effective technology.

One other issue should be mentioned before we proceed with the analysis. In determining whether a technology has crossed from experimental to state-of-the-

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how you are approaching this issue? You said judges are faced with the fact that they have two opposing medical experts and therefore do not know how to make the judgment, so they automatically find in favor of the patient. That is probably not in the patient's best interests in some cases. Is the American Bar Association beginning to approach this issue of effectiveness?

A: [Mr. Stein] I cannot speak for the entire legal profession. I think, as there are conflicting and opposing medical experts in an advocacy system, there are also opposing legal experts who under the canon of ethics have a responsibility to defend their client zealously. Zealously defending their client may not be, as you would put it, in their client's best interest.

If the client believes, however, that he or she is entitled to certain kinds of care and arguments can be made on that person's behalf the way the system is currently set up, each side is going to argue as effectively as he or she can in pursuit of that particular client's perspective, which may be—and I do not think it is complete heresy for a lawyer to make this statement—that sometimes the courts are not the best place to resolve these issues. There have been efforts by the judicial conference and a number of other groups to assist judges by helping them to better understand science and the way in which science is described so they can make determinations.

What does help, however, if there is not one single clear voice, is more of an assist from the scientific and medical community as to what the community believes to be safe and appropriate or safe and effective. In that way, the judge has something to fall back on—something to look to and a more impartial opinion than that of the experts who are there because of their expertise but at the behest of a particular side.

Q: [William Rutt, Henry Ford Health System, Detroit] My question is for Dr. Freeman. It has been popular to speak of patient preferences. If poor people in a community were to be meaningfully and continually involved in decisions about resource allocation for health care in their community, would they spend it differently than they now spend it?

A: [Dr. Freeman] That is a very tough question to answer, since it has never been tested. Poor people in general do not have much of a voice with respect to their own economics.

Q: [Dr. Cova, Health Insurance Association of America] I would like your opinion as to whether the American people are willing to bear that kind of burden, particularly when sociologists keep pointing out that the top 20 percent of the people in our population—the affluent—are becoming more and more disconnected with those in need. They do not identify with them. We have to think about these things in a much broader perspective; would you address this issue?

A: [Mr. Stein] I am very sympathetic to the issues that you raise because I think they are important, but I must return to something I said earlier. It really depends on where this particular 2-day session wishes to put its focus. You are not going to be able to solve the problems and resolve the issues you have raised. I am not sure that we are going to be able to address the issues any more than we can answer one of Dr. Freeman's questions—should we put more emphasis on insurance for preventive therapies and procedures than we do on curative treatments, and would we be better off then? I know a debate has been going on within a variety of industries about this issue.

In terms of what the political perspective has to offer, the result is going to be that both private as well as public payers will ration care—and every society has to ration anyway—and it will not matter whether it is a universal program or not. When that starts to hit home to more people, then they will sit up and listen and say, "Well, is there another way?"

I am not that sanguine to think people will look at things too far ahead of time. One of my favorite sayings is an old Pogo statement: "Man never sees the handwriting on the wall until his back is to it." I suspect that is what we are going to be doing in this area also. One can just question whether we are there already.

A: [Dr. Freeman] I appreciate your comment, and at a meeting that was held a couple of years ago with respect to what insurance companies would offer for screening mammograms, the insurance companies' point of view was clear. They will offer whatever you pay for. That is a simple statement, and there should be no argument. It is a business. Insurance companies are not in business to solve social problems. They are in business to keep in business, and hopefully they can do some good while they are at it.

I do not think we should say the burden is on the business. The burden should be on the American public and the policymakers in America to solve the problem, but I think there is some hope because we have interesting bed partners now—more interesting than ever. When Lee Iacocca is in the same bed with the uninsured, this is a very interesting set of bed partners.

The corporations of America are being thoroughly tested with respect to their ability to pay for health care for their employees. Lee Iacocca must compete with Japan, which probably does not pay nearly as much for health care for their employees. So we are beginning to get a situation where the middle class is also being affected by this problem as the problem moves upward. Unfortunately, the solution is going to come based on those kinds of happenings, and if it remains just confined to the poor population, the problem probably will not be solved. However, now that the large corporations and middle classes of America are feeling the pinch, I have hope.

Although I don't like the situation, I think it offers the possibility of solutions. I suspect that within the next several years, there is going to be a major change in health care coverage for all American people. I do not know which way it is going to go, but I think it is going to be a very major change.

A: [Dr. Holohan] I would add that I do not know how much the American people are willing to pay for health care. There have been a series of surveys trying to assess that very question, and the results have always been inconclusive. As far as the question of equity or distributive justice, the first question I posed—a question, not a statement—was do we as a society believe that every person has a right to health care? I do not think we have answered that question yet.

Q: [John Freedman, ITT Hartford Insurance Group] This country has never been known for being able to equitably distribute any of its assets. With that in mind—together with the notion that developing new technologies and the price tag attached to them, although advancing the cause of science, become increasingly unavailable to people—is there an ethical burden on the research and development part of medicine to perhaps slow down and require the rest of society to catch up in its ability to distribute these technologies and services to the vast majority of people?

A: [Dr. Holohan] First, I do not think that it is ever going to be possible to slow down technological change. Probably the most significant retardation would be by decreasing the availability of funds for research. Even so, I personally believe that it would be a pyrrhic victory.

It is not entirely clear to me nor apparently to the Prospective Payment Commission as to how much new technology, in fact, costs in the long run. I do not think that has ever been approached. I have seen arguments raised by proponents of an innovative treatment that, in fact, it does not cost more than standard care. To my knowledge, that has only been evaluated once in an article published in the *New England Journal of Medicine* on the cost-effectiveness of bone marrow transplantation. The data were fairly clear; bone marrow transplantation is, in fact, cost effective.

Now, that requires an unusual set of circumstances in that patients who are given standard therapy in lieu of innovative therapy would linger for a particular period of time. It would be likely to be the case, for example, in Hodgkin's disease where patients would die, but they would not die very fast. They would die slowly while consuming large amounts of resources. You probably could never show that for something like metastatic carcinoma.

A: [Dr. Freeman] I heard a Senator say that in the last 28 months, we have spent more on military research and development than we have since the turn of the century on medical research. So, I have a feeling that we may be at a turning point in America. Many walls have come down. The Iron Curtain has melted. The Berlin Wall is down. Things are happening around the country and around the world that would perhaps convince many we do not need to continue to spend billions of dollars on defense as we have in the past.

If this logic holds, then maybe the country can put more money to social causes including medical care. We do not need Stealth bombers now as much as we did before. As a matter of fact, I say we do not need Stealth, we need help. I think we have an opportunity, and perhaps this is a historical moment when billions of dollars could be transferred to social programs. In fact, if we as a country do not do that, we might even have a period of unrest because people are getting a bit impatient about the things that are happening. The homeless are increasing; the middle class is being affected and not able to get adequate health care.

I honestly think that a country like this has enough money to continue strong research capability to transfer technology to all American people and still move ahead. We have a country that is wealthy. We need the political will to do what is right.

Perspective from the National Institutes of Health

John H. Ferguson, M.D.

Virtually all of the institutes at the National Institutes of Health (NIH) are involved in research on some aspect of medical procedures or therapies that fall in the continuum from experimental to state-of-the-art. Indeed, a basic mission of the NIH is the discovery of these health technologies and the research necessary for their progress from the bench to the bedside. In that portion of the continuum where the technology is evaluated in patient populations, often with clinical trials, the attempt is made to distinguish "experimental" from "state-of-the-art" for reimbursement purposes. These decisions are generally made after the appropriate trials have been conducted.

For the purposes of this discussion, it is useful to consider four categories of medical technologies: therapeutic, diagnostic, preventive, and adjunctive. In the therapeutic category, we will consider medical and surgical divisions. In the diagnostic category, one might consider invasive and noninvasive procedures as subdivisions. In preventive technologies, we will follow the Guide to Preventive Services categories of primary, secondary, and tertiary. Primary prevention is for asymptomatic individuals—for example, routine immunization. Secondary prevention is to identify and treat those who are asymptomatic but have already developed risk factors or preclinical disease—for example, Pap smear to detect cervical dysplasia. Tertiary prevention is the application of preventive measures in symptomatic individuals—for example, insulin treatment in diabetics to prevent complications of diabetes. The adjunctive category might include various devices like hospital beds, braces, intravenous tubing, and so on.

A continuum from inception to state-of-the-art exists in all these categories and subcategories. Although the idea of the continuum is the same for all categories, the continuum itself will differ in many respects from category to category and should be approached accordingly in the decisions relating to when experimental becomes state-of-the-art for reimbursement purposes.

As a preliminary overview of the continuum for discussion, some steps will be defined employing a scheme that can be used as a straw man for modification and criticism.

- **Inception** — The safety or effectiveness of the technology is regarded by the evaluation community as untested.
- **Innovation** — The safety or effectiveness of the technology is undergoing preliminary testing.
- **Investigation** — There is insufficient evidence to determine the safety or effectiveness of the technology. Use of the technology in patient populations should be confined largely to research protocols.
- **Promising** — Given current knowledge, the safety or effectiveness of the technology is appropriate for some indications in certain patient populations.
- **Established** — The technology has been adequately evaluated for safety and effectiveness for given indications in specified patient populations.
- **Guidelines** — The technology is accepted as routine and a standard of care for given indications in specified patient populations.

Several issues require special emphasis. Once the provider is reimbursed by a large or major payer, in general, the use of a technology will spread. Therefore, it behooves those responsible for the health and safety of our citizens—public health in general—and for the use of resources to make the reimbursement decisions carefully. To spread an expensive treatment or diagnostic test among our citizens might be beneficial in the long run if the health outcomes are positive and clear. If not, we are spending precious resources for marginal or no health benefit which we can ill afford.

One should mention the "flip-side" of reimbursement for "established" technologies; that is, stopping reimbursement for a technology determined no longer to be safe or effective or to have clearly been replaced by a newer, safer, or more effective technology.

One other issue should be mentioned before we proceed with the analysis. In determining whether a technology has crossed from experimental to state-of-the-

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art and is therefore reimbursable, one should judge the quality of the evidence on which the decision is based. A readily available protocol has been used by the Canadian Task Force and the U.S. Preventive Services Task Force.

The present analysis will concentrate on the therapeutic and diagnostic categories. Arguments could be made that efforts should be concentrated in the preventive arena. Given scarce resources and the fact of serious disease burdens, there is a societal sense of urgency for the treatment of these very desperate conditions. Although treatment must follow diagnosis, the urgency appears with the diagnosis. A new diagnostic technology—although exciting and possibly important in allowing earlier diagnosis and treatment or even secondary or tertiary prevention—does not generally carry the same sense of urgency. Should one then apply different standards or rules for the determination of experimental versus established or state-of-the-art for therapeutic technologies from those applied for diagnostic modalities? Should yet another set of standards apply for surgical therapeutic technologies? It is suspected that different standards and rules already apply de facto to surgical therapies.

In the following discussion, therapeutic and diagnostic technologies will be treated separately as they should be. Therapeutic technologies for serious disorders will be treated differently than therapies for less life-threatening diseases and differently than surgical therapies. Preventive technologies, especially primary preventive technologies—for example, vaccine development for acquired immunodeficiency syndrome—certainly deserve yet another approach. It is clear that preventive technologies have historically been, and continue to be, approached differently by the medical profession and certainly by third-party payers, not always to the advantage of society.

In the present schema, we would consider that the experimental side of the continuum begins at "inception" and extends to somewhere in "investigation." State-of-the-art might begin for some treatment modalities in the "investigational" portion of the continuum.

A number of factors should be considered for any of these continua, whether diagnostic, treatment-related, or preventive. They are:

- Nature of the illness
- Number of patients or people involved
- Prevention is preferable to cure
- Cost
- Expected benefit
- Quality of life
- Is an adequate alternative available?
- Will reimbursement: (1) spread the use of the technology? (2) prevent a clinical trial from taking place; (3) prevent patients from entering a trial; or (4) prevent patients from being assigned at random?
- Once the technology is reimbursed and being performed: (1) can one study the technology in controlled trials? and (2) is it ethical?
- Regarding drugs: (1) if it is an "experiment," insurers will not pay and drug companies must bear the cost of the trials and care; and (2) if it is a "treatment," insurers will pay, and drug companies (sponsors) can charge for the drug.

The argument that the decision to reimburse should be moved toward the experimental side of the continuum for conditions that are life threatening, desperate, life shortening, or crippling and for which conventional therapy does not exist or has failed is appropriately made by several of the NIH institutes. It is not difficult to accept that we as a society owe our sickest citizens safe and effective treatment for desperate conditions. The questions are who pays for this and how and by whom is safety and effectiveness determined?

We at the NIH would like to suggest that for certain diseases as described, and under clearly designed and defined protocols, insurers could reimburse for treatments that might heretofore have been considered experimental. When these are, in effect, the only treatments available, and the conditions for careful control of peer reviewed treatment protocols are met such that data may be captured for appropriate scientific use, then all parties stand to gain. This would include patients, providers, investigators, research sponsors, reimbursers, and society at large. This would mean that insurers would bear the cost or part of the cost of some portions of clinical trials. It should be pointed out that the numbers of patients involved in trials of these kinds are often not large by comparison with the total numbers of patients. For instance, the National Cancer Institute (NCI) notes that the number of patients per year in NCI-supported trials is about 30,000. The financial burden may not therefore be excessive, compared with that if all patients with the condition were to be reimbursed for the proposed treatment.

Furthermore, the opportunity would exist for insurers to have more influence over the conditions of reimbursement. Targeted and controlled expenditure now, before "the horse is out of the barn," might save millions in the future and provide better health. Ineffective, unsafe, and possibly very expensive therapies can be eliminated earlier in the continuum before generalized reimbursement has encouraged widespread use. Finally, with reimbursement coming from those with more experience in tight fiscal control, investigators would be encouraged to pay attention to economic end points.

Many insurers now pay for the care of patients with these conditions, some of whom are involved in clinical trials, and it is often difficult to separate the incremental care necessary solely because of the experimental protocol from that which would be necessary because of the underlying disorder. If insurers accepted what we are suggesting, this dilemma might be resolved at least in part. For reimbursement purposes, the definition of surgical and diagnostic procedures as experimental or state-of-the-art care for less desperate or chronic conditions is in some ways more difficult.

Surgical procedures appear to continually evolve such that what may actually be quite new and innovative would still be reimbursed because it was done for an accepted indication. The fact that a new instrument (for example, a laser or laparoscope) was used for an accepted surgical procedure may or may not be important to the insurer in determining reimbursement. One suspects that as long as the bill submitted is less than or equal to previous similar procedures, it may be reimbursed. Laparoscopic cholecystectomy may fall into this category. On the other hand, laser photocoagulation for certain retinal disorders required trials, as a new instrument was used in a new procedure for a new indication.

New diagnostic tests have not had a stellar record of vigorous scientific trials before being accepted as state-of-the-art and being reimbursed. Virtually all of the NIH institutes are involved in one way or another in the development and testing of many of these devices or laboratory procedures. All recognize the necessity of rigorous technology assessment for safety and efficacy when applied to human populations. It is suggested that there is little sense of urgency (in the medical/health sense), and therefore there is time for adequate assessment before reimbursement.

The major point of emphasis is that the distinction between what is experimental or investigational and what is established or state-of-the-art can only be made by testing and careful assessment by unbiased groups and processes. Thorough technology assessment can move a technology along the continuum from experimental to state-of-the-art or determine it to be unsafe or ineffective. One would like to keep the innovation pipeline full at the input end but be selective and discriminating at the output end, choosing only those technologies that improve health. This selection from numerous choices requires numerous assessments. It is unlikely, nay, impossible, that the Federal Government could fund all the assessments necessary for all the health technologies that continually flood the pipeline attempting to reach the market. The burden of cost for these assessments might be shared among Government and the private sector, including industry and professional groups. The Federal Government, being it is hoped the least biased in a promotional sense, might be able to coordinate this effort.

Many methods are available and should be used. Obviously, the medical literature searchable by computer is easily accessible. The gold standard remains carefully planned and executed clinical trials. Group judgment methods are used by many organizations such as the American Medical Association, American College of Physicians, RAND, Health Insurance Association of America, and others. Obviously, we think that the NIH Consensus Development Program has evolved with such care that the results of these deliberations are "tailor made" to help solve some of these questions where "experimental" meets "state-of-the-art." We have attempted to ensure unbiased evaluations in a public forum of controversial issues for which data are available.

Certainly, the processes used by the Office of Health Technology Assessment, Office of Technology Assessment, and Institute of Medicine can offer important information in making these determinations. These reports are all publicly available and should be used. The process used by the U.S. Preventive Services Task Force and before that, the Canadian Preventive Services Task Force, with their careful attention to grading the strength of evidence of the literature on which they based their conclusions is an extremely important example of how the existing literature can be graded for use in these types of decisions.

Lack of data, lack of good data, and the quality of data on which to base health technology assessments are major problems for all of us involved in these endeavors. One might wonder why the insurance industry, which clearly obtains and uses a great deal of health information, cannot share this with health technology assessors. The reasons are both legal—namely, antitrust—and proprietary—namely, trade secrets. Some process should be encouraged whereby NIH and society at large could all use and benefit from the entire universe of health information, including that gathered by third-party payers.

We must remember that insurers handle claims and are asked, in effect, for "go, no-go" decisions. The complex health care, legal, public, societal, and competitive environment in which they operate makes these decisions difficult. Our own study of court involvement in these cases—ordering insurers to reimburse for such ineffective and unsafe treatments as laetrile and immunoaugmentative therapy and to pay for thermography, an expensive, unproven diagnostic procedure—makes us especially appreciative of their dilemma. They are not likely to win many of these cases. This may clearly affect a decision to reimburse before adequate assessment has occurred. Nevertheless, we as a society, both from the health as well as the economic standpoint, cannot afford health care that has not been assessed.

Some kind of task force composed of representatives such as those attending this conference should meet to define and refine the terms that are being used. The definitions of many of these terms such as experimental, investigational, established, state-of-the-art, and so on need to be agreed on or appropriate substitutions made for this type of endeavor to go forward. A similar group could provide input for planning a more global health technology assessment effort.

Perspective from the Medical Colleges

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The perspective of the Association of American Medical Colleges (AAMC) is that of the private sector in the sense that the medical schools the AAMC represents are part of the private sector, even though two-thirds of the medical colleges are State schools and only one-third are private. In addition to representing the medical colleges, the AAMC also represents the teaching hospitals that are such a necessary part of the American medical education system. They are important in the context of this conference on experimental versus state-of-the-art technologies, since it is in these teaching hospitals that many state-of-the art technologies are developed, tested, and refined. The three missions of teaching hospitals are patient care, clinical education and clinical research, and the dissemination of applied technology. Although these missions are closely intertwined, it is the last one I want to address.

In general, medical research can be divided into three phases: basic research, clinical research, and applied research. Defined rather grossly, basic research identifies the fundamental properties of living matter. It is laboratory based and occurs primarily in universities and private and public research institutes. In a few cases, teaching hospitals have developed basic science capabilities as well.

Clinical research, by the definition I want to use, applies the findings of basic research to explore diagnostic and treatment ramifications or deals with the exploration of clinical phenomena, even when basic knowledge concerning them is lacking. Clinical research may involve studies on animals and humans. Animal research generally takes place in a university or research institute laboratory, whereas patient research usually is carried out in teaching hospitals or clinics or in defined populations not confined to or monitored in health care facilities. Here the hospital, clinic, or institutional data-gathering agencies serve as the laboratory.

In the third phase of research—clinical application—the new diagnostic or treatment technology is studied at a relatively few sites, and the involved teaching hospitals apply the new technology or procedure to a growing number of patients. During the past 50 years, the medical sciences have made dramatic advances in diagnosis and treatment. Many of these advances began in the basic research laboratories of universities and were transferred to clinical settings as part of research programs in teaching hospitals. Major teaching hospitals offer a natural venue for the advancement and early application of medical knowledge by bringing together seriously ill patients and the research-oriented physicians who comprise the faculty and staffs of these hospitals. This cast of characters falls under the purview of the AAMC, and interest in technology transfer is a very real part of the association's agenda. In this context, I would like to address the following issues:

1. The effect of the external environment and the application of new technologies;
2. The funding of clinical research;
3. The evaluation of new technologies;
4. The role of cost and the use of cost-benefit analysis in assessing new technologies; and
5. The dissemination of new technologies into practice.

In terms of the external environment, against the current background of cost-containment and competition, academic medical centers have come face-to-face with dazzling advances in the technology of biology and medicine. These changes have profound economic, social, and public policy implications. For example, how far should we employ genetic techniques to alter heredity, sex, the aging process, and indeed, the very nature of life? What should be the cost to society of the technological advances that permit dialysis and transplantation for every patient with renal failure or revascularization of the coronary arteries for everyone in whom the disease can be diagnosed? And what should be the cost of

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allowing almost indefinite life with the aid of life-support systems? Although the benefits derived from these advances are often clear and convincing, their contribution to health care costs cannot be ignored.

Along with the issue of cost-effectiveness are concerns about the manner in which medical technology is introduced and disseminated. No system has yet been developed to assess medical technology from the standpoint of either efficacy or cost-benefit. Moreover, although there is a great tendency to introduce new technology into the health care system, there is great hesitation to eliminate medical practices once they have become obsolete. The introduction, evaluation, and cost of technology are becoming progressively more troublesome problems for our society.

The problems facing the health care system with respect to experimental diagnostic and treatment modalities are several and raise these questions:

- First, by what process are experimental treatments and diagnostic technologies funded during their developmental phase?
- Next, by what process are they evaluated for effectiveness and efficacy?
- Third, what role does cost-benefit analysis play in such an evaluation?
- Finally, at what point does an experimental regimen become recognized as a routine part of the physician's armamentarium, and what are the cost implications of such recognition?

For decades, the Federal Government has been the primary source of funding for biomedical research through the National Institutes of Health (NIH). During much of the post-World War II period, this country's biomedical research enterprise prospered and grew at a steady pace. During the last decade, however, a number of concerns have developed that have an impact on the issues before this conference. Competition for grant funding is becoming more fierce, and there is an increasing perception in the scientific community that research is no longer a growth industry. This is particularly true, it appears, for physicians contemplating careers in clinical research. The emphasis at NIH has been on elucidating basic biomedical events, and there is a perceived tilt away from the physician-investigator interested in clinical problems in favor of the basic biomedical scientist. Federal funding for clinical research is not keeping pace with the growing need.

When NIH does fund clinical research, it usually assumes the costs only of what it defines as the research portion of such an investigation. Clinical research, however, by its very definition includes a patient-care component, for which NIH expects others to pay. Likewise, the pharmaceutical industry spends nearly a billion dollars annually for clinical trials but often expects others to pay for the patient care involved in those trials.

The majority of private insurers exclude experimental or unapproved therapy from coverage altogether, as does the Medicare program. Too often decisions are made on a case-by-case basis, prompted by the glare of a media campaign on behalf of a single afflicted individual. As a recent *New England Journal of Medicine* "Sounding Board" article put it, "The persistent, litigious, or persuasive patient is more likely to receive the possibly experimental treatment with this system. The meek shall not inherit the treatment."[1]

The absence of a payer for the patient-care expenses during the development of experimental treatments and technologies has an adverse impact on our ability to mount effective clinical research projects. The Association of Community Cancer Centers reports that although more of its members are participating in clinical trials, the number of patients enrolled is at a plateau.[2] Some look to the Government to mandate third-party payment of experimental treatments, but this is unlikely to happen. Medicare payments are subject to stringent budgetary controls as the Federal Government tries to deal with an increasingly intractable deficit. The basic premise of the insurance industry is to spread known risk, and the industry is ill-equipped to provide coverage for treatments that it had not even considered in developing its premium structure. Moreover, even if third parties were mandated to assume the cost of new treatments, the more than 35 million Americans who have no insurance would remain uncovered.

In terms of evaluation, the process by which a new drug or device moves from experimental and investigational to proven and approved, although often painfully slow, is relatively clear-cut and well understood throughout the community. The process for a similar dissemination of a diagnostic technique or treatment modality is less well-defined but is just as important in the consideration of the differentiation between experimental and state-of-the-art health care. A serious problem exists because technological advances outpace the ability of medicine to evaluate them in a scientific manner. The new discipline of health services research must be invoked to assess and evaluate new techniques, document their contributions to improving health and the quality of life, and monitor their dissemination into mainstream health care.

Only relatively recently has medicine come to accept health services research as a valid academic discipline that can contribute to the overall mission of academic medical centers. The term "health services research" encompasses a wide variety of investigational techniques and objectives and includes such activities as medical decisionmaking, appropriateness review, outcomes research, quality assurance, and organization of medical care. These are developing fields in medicine, but ones that are still woefully inadequate to the task. This country desperately needs to build an infrastructure in which to carry out health services research, much like that which has been built for biomedical research in general.

Currently, we are wallowing in a sea of poorly defined problems studied in diffuse contexts by an undermanned cadre of research workers. Health services research is often poorly funded and sometimes not funded at all. Despite the creation of the Agency for Health Care Policy and Research (AHCPR), the agency sponsoring this conference, there has been little Government money in support of it, and help from the private sector is sporadic at best. Perhaps most importantly, the people trained to work in this difficult and complex arena are not available. An infusion of physician-researchers is needed if the field is to prosper. The medical profession's view that decisions about new diagnostic tools and new therapies should be left to the medical community is essentially correct, but this will not occur unless physicians can develop better and more generally accepted criteria for recommending the use of new modalities.

This involvement must occur through the academic medical centers, but to date, these centers have not assigned a rightful place to health services research in the academic reward system. This must happen if academic institutions are to attract the best minds to this field. Appointments' and promotions' committees must realize that this new field will require different criteria for academic advancement than do the traditional scientific disciplines. Population-based studies will necessarily require a longer time for completion and are likely to result in fewer papers, perhaps published in journals that are foreign to a traditional medical school faculty committee assigned to evaluate a health services researcher.

Although much of health services research must be carried on in academic institutions and private public policy research organizations, the AHCPR must be in the forefront of providing the national leadership for evaluative information and analytic capabilities in technology assessment and is moving toward that goal.

Cost-benefit analysis presents another cause for concern. Many believe it will be an important factor in evaluation of health care technologies for effectiveness and efficacy, but my view is that it may not be the clarifying tool that its supporters hope it will be. Cost-benefit analysis is not a subject with which most physicians are comfortable. First, they are not trained in its intricacies; rather, they give primacy to securing the welfare of their individual patients. A physician's instinct when confronted with an acutely ill patient is to try everything to alleviate that patient's suffering, even if a total cure cannot be achieved. A theoretical cost-benefit analysis remains just that—theoretical—in the face of the pressing need to cure or ameliorate disease.

It is becoming clear, however, that issues of cost must become a more integral part of medical decisionmaking. If physicians are unwilling to participate in developing a consensus on the appropriate role costs should pay in selecting therapy, they are likely to find others, more distant from the patient, who are willing to make those decisions. It is my hope that physicians will become more involved in the health services research that will shape such decisions.

Cost-benefit analysis will conceivably be used in two ways to influence reimbursement. The first will be to assess the competing treatments available for a particular disease in an individual patient. An example is the use of 5-α-reductase inhibitors in the treatment of prostatic hyperplasia. This drug will become available under the name "Proscar" sometime in 1992. It will obviate prostatectomy in about two-thirds of patients with prostatic hyperplasia but will require lifetime treatment; individuals who do not keep up with the drug will experience a recurrence of their problem. The patients will have a choice, but in a managed-care setting, will that choice be permitted? A second and more difficult application of cost-benefit analysis occurs when expensive technologies are pitted against more mundane services, even though the "high-tech" methods will only palliate and not cure. The restriction on transplants by Medicaid proposed in Oregon is a good example.

The *Washington Post* ran a front-page story (Sept. 1, 1991) entitled "Organ Transplants: Rationing by Wallet?" The reporter commented on regulations proposed by the Health Care Financing Administration that would explicitly mandate that cost-effectiveness be considered in coverage decisions. Gail Wilensky is quoted as saying that the proposal is not meant to block "something that is a great advance just because it costs a lot," but instead would allow Medicare to pay no more for a new treatment than for an equally effective older one. The article also raised the ethical issue that there is still "a debate over transplants—and other expensive medical procedures—and whether their costs can be justified in terms of the relatively few who benefit."

How accurately can cost-benefit or other economic analysis be applied to clinical problems? Alan Hillman and his colleagues[3] at the Leonard Davis Institute of Health Economics have written:

> Economic analysis is a new, evolving, complex, and unstandardized field with which many editors, reviewers, policy makers, physicians, and universities are unfamiliar....Existing university policies to protect academic integrity are less able to detect and prevent bias in such studies than in other forms of research. In economic analysis, the choice of which agents and interventions to compare, which data to include, which costs to measure, which perspective to adopt, which outcomes to assess, which assumptions to make, and how to present the results may produce important differences in a study's conclusions.

Looking at the dissemination of new technologies into the medical care system, we see that it is unrealistic to expect that we can identify the point at which a treatment ceases to be experimental and becomes universally recognized as routine. The American Medical Association's Council on Scientific Affairs[4] defines this dilemma most succinctly: "Technologies develop along a continuum of accumulating evidence about their safety and effectiveness." Although it is certainly desirable to prevent the premature diffusion of a complex and expensive technology, it may be difficult to gain consensus on clinical utility and appropriate applications.

Currently, it appears that the decision is in the hands of decentralized third-party payers whose policies on reimbursement for certain technologies are the de facto determination of whether a treatment is still viewed as experimental research. Experience has shown, however, that experimental therapies that are less expensive or that do not involve inpatient care are released from experimental status more readily and earlier in their existence. Obviously, different evaluation standards are being applied, and cost seems to be an important component in such decisions.

A rational approach would seem to be to seek medical consensus on the effectiveness of a treatment, and that once reached, such consensus should be sufficient to assure third-party reimbursement for that treatment. It is more difficult to describe the process by which such a consensus should be reached because professional medical specialty societies are often not in agreement. Moreover, many groups would like to go further than consensus. For example, the National Cancer Institute (NCI)[5] advocates that "in the treatment of cancer, patients on clinical trials receive therapy that is quite likely to be at least equivalent to or possibly better than standard treatment." Here, the NCI promotes the concept that clinical trials represent standard treatment for cancer patients where no cure is known to exist.

In conclusion, these are difficult issues with which our health care delivery system must grapple. The AAMC's member medical schools and teaching hospitals are the loci where many of the experimental therapies are tested and applied. The uncertainty of payment mechanisms for these treatments is a real and critical problem for these institutions as they pursue dual missions of advancing knowledge and caring for patients. As leaders in America's health care delivery system, however, these institutions must also accept responsibility for developing solutions to the issues involving application of new technologies. It is for this reason that the Association of American Medical Colleges is pleased to be included in this debate, and we thank AHCPR for initiating these discussions.

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Practitioners' Perspective - I

H. Denman Scott, M.D.

Many doctors and patients do not see a clear distinction between experimental and state-of-the-art, especially in circumstances of serious illness, but is the line between the two so fuzzy as to be always indistinct? Is it possible to draw a clear line, at least in some circumstances? In my opinion, it is. In a health care enterprise which is so robust, so vast, so entrepreneurial, and so good at exciting the public, will anyone pay much attention to the lines we draw? Or will the momentum inherent in a $700 billion activity push past any logical checks and balances?

The circumstances that the practicing internist faces—and one that I faced many times during my years of practice—is a patient, usually in a life-threatening circumstance, with a very advanced disease. Usually, the patient has a malignancy or, over the past few years, acquired immunodeficiency syndrome.

Many technologies are readily available—single drugs, new drug combinations, bone marrow transplant, plasmapheresis, and so on. The probabilities of success are often low, but if the treatment works, results are sometimes quite spectacular.

In these circumstances, there is always a sense of desperation. The physician wants to offer some hope. The patient clings to whatever is offered. The doctor really wants to do all that he or she can reasonably do. The decisions made are not mindless. They are very carefully considered by a whole range of people including the patient who is so sick. Decisions are also strongly influenced by the presence of health insurance which insulates both the patient and the doctor from the economic consequences of various treatments.

When insurers resist paying for treatments they consider experimental, the patient, sometimes the patient's doctor, and others turn to television to plead their need. The story of human suffering against big bureaucracies evokes public sympathy, and often the insurer will cave in to this outpouring of concern. I always feel sorry for the insurance company medical directors who must explain to the TV audience why various statistical data or lack thereof justify withholding a treatment from a gravely ill person. If the insurer continues to resist, as we have heard earlier, patients, their lawyers, and their families commonly resort to the courts which often side with the patient.

Thus, in the media and in the courts, the individual perspective predominates. More complex and subtle societal issues about cost-effectiveness and the problem of excessive health costs are pushed into the background and put off until another day.

In the United States, health care operates much of the time on a piecework basis. We take care of people one by one. Not enough of us ask the question, "What is good for the population as a whole?" This failure to reflect on and understand the public health perspective has allowed the health status of the Nation to deteriorate.

As clearly highlighted by Dr. Harold Freeman at this conference, we see an appalling failure to provide primary and preventive care to millions of Americans. Thus, we see resurgent measles epidemics of unusual virulence. We see tuberculosis making a comeback. We see much more gonorrhea and syphilis. We see people untreated for asthma, diabetes, and hypertension. We see pregnant women without prenatal care.

The problem with access in America is not that the acutely ill person or the poor woman with a massive breast tumor does not eventually stumble into the system. The problem is that people are not welcome into it, and as a result, they are being deprived of well-established, highly effective state-of-the-art treatments. A measles vaccine is a brilliant intervention. Insulin, of course, is old state-of-the-art. There are many more treatments that those who lack access to care do not receive in a timely fashion or do not get at all.

Our failures in health care are having serious consequences. We see more learning problems in the schools. We see greater burdens imposed on our schools because of these learning problems, and we see a less able work force in our future because of this neglect.

Coping with these problems is essential to the public health and a productive society; our failure to deal with

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them will inevitably lead to a weaker society. Therefore, it is very important to deal with the problem of state-of-the-art versus experimental. We should not waste resources on ineffective care.

Can we create a mechanism to test the untested in the course of our everyday medical practice? We urgently need to expand and create programs and incentives to attract first-rate talent into the field of health services research. Even with an expanded budget for the Agency for Health Care Policy and Research (AHCPR), the resources are relatively vestigial. Compare the AHCPR's budget of $120 million with $9 billion for the National Institutes of Health (NIH), $120 billion for Medicare, and $100 billion for Medicaid. Relatively, health services research has a thimbleful of resources devoted to problems of such great interest and importance. We all should urge increased funding for health services research from both the public and private sectors. With greater resources, we can think about creating national mechanisms to determine which therapies and which diagnostic strategies should be declared experimental and evaluated in practice.

How can we establish a list? We can canvass our insurers. They are dealing with contentious issues day by day. We can follow promising research and, before a therapy becomes widespread, can test it in different settings.

One option would be to develop a community testing network—something analogous to the human immunodeficiency virus (HIV) experience. Many problems have occurred during the HIV community trials. These need to be understood and new approaches devised. The approach should not be abandoned.

As we seek knowledge of what is effective, one of the great challenges will be to sustain innovation. Bureaucratic inertia can be stultifying and impede the whole enterprise. Although some bureaucracy is a necessary fact of organizational life, we must constantly seek ways to minimize its adverse effects.

Consider the issue of laparoscopic gallbladder surgery. It was invented in France and imported to the United States by a private practitioner in Tennessee. Surgeons traveled from all over the Nation to learn the new technique. Patients who had the procedure found themselves going home in 1-2 days without a big scar and with few discomforts. Almost overnight, an industry was created. Surgeons are now taking their scopes, cameras, and other new tools into other body cavities and performing remarkably complex procedures.

This surgical revolution bypassed the ordinary developmental process in this country. Academic centers, medical schools, and NIH funding were not prominent. Also not prominent was any early systematic evaluation of effectiveness and complications. This was and is a serious failing in this particular circumstance.

We must work towards the marriage of innovative energy to early and careful evaluations of the innovations. We need a set of rules that can help us with these problems and, at the same time, structure ourselves so that the innovation is not slowed down unduly.

What if laparoscopic surgery had to get Government agency approval? With luck, it might be part of the Nation's Year 2000 Health Objectives. In short, a 10-year bureaucratic drag could have occurred.

On a closing note, let me tell you about an experience I had in private practice. One of my patients was a bishop, and he had a way of tweaking me out of my routine thinking. On one occasion, he asked, "How would you be caring for me if we were 500 years into the future?" For one struggling from week to week, this drew me up short. "Is it right," he asked, "for you to invest so much in me to gain a few weeks or months of life when so much need exists among so many whose lives are largely ahead of them?"

Surely, what we do in the next 100 or 500 years is bound to be different from what we are doing today. It is unlikely that our society will continue to devote an ever-increasing amount to medical care, given the whole societal agenda before us. Since 1950, as you all know, the proportion of resources given to medical care has tripled from 4 percent to 12 percent of the gross national product. Consider the next 40 years. Will it triple again to 36 percent of the gross national product? Probably not. What will we be doing and how will we shape what we do? Important questions for today, crucial questions for tomorrow.

Practitioners' Perspective - II

Elizabeth Brown, M.D.

This paper will focus on defining the term "investigational" because this issue is faced every day in the Division of Health Care Technology of the American Medical Association (AMA). We receive calls from payers, patients, and their physicians and lawyers all asking about medical services and really wanting to know the answer to one simple question—or one they believe is simple—is this service investigational or not? The underlying reason behind the calls is always the same. The callers want to know prospectively whether this medical service will be covered or retrospectively why it was not covered.

Many of the callers would like to think that the AMA or some organization should have a master list of what is or is not experimental or investigational and that the answer to the question should be as simple as consulting this list. Of course, it is not that simple. Our callers are always asked their definition of investigational or experimental, and more often than not they really have no idea.

Why has this issue become so important? The reason is primarily that investigational as an exclusionary criterion for insurance coverage has been exercised increasingly in this era of proliferating health care technologies and increasing health care costs. Therefore, it is a serious issue and, for some patients, a matter of life or death.

For example, preadmission denials often appear as denial of care. Faced with this, patients challenge these decisions in court. Legal challenges to coverage denials of high dose chemotherapy and autologous bone marrow transplant for breast cancer have become common; and when the courts are given the opportunity to weigh the evidence themselves and determine whether a service is investigational, they typically find in favor of the patient.

These court cases illustrate that the definition of investigational or experimental can be looked at in three ways. First, we look at how the word investigational is defined. Second, we examine the process by which it is determined whether a medical service does or does not fulfill that definition; this process involves technology assessment—that is, the coverage decisionmaking process by third-party payers. Finally, the issue quickly evolves into a bigger discussion of the underlying policy question—is the use of the term "experimental" an appropriate way to exclude coverage for medical therapies?

We elected to examine how physicians define the term investigational. In our technology assessment program at the AMA, which is called the Diagnostic and Therapeutic Technology Assessment Program, referred to as DATTA, we routinely survey physicians and ask them to evaluate the safety and effectiveness of technologies. One possible rating the panelists may select is investigational, which is defined as follows: "There is no consensus on the safety or effectiveness of this technology to date. There is insufficient evidence to determine its appropriateness or if it warrants further study or if the use of this technology for the given indication in the specified patient population should be confined to research protocols."

We wanted to find out what our panelists thought of this definition and how they interpret other commonly used definitions of the term investigational. The study question is summarized as follows: Is there a difference in the use of the word investigational in different clinical settings and in different contexts?

The two different clinical settings were patients with terminal illnesses and patients without terminal illnesses. We wanted to test the hypothesis that there is a different interpretation of the term investigational for those patients who have a terminal illness and for whom treatment options are limited. The two different contexts in which the term investigational is used were in the medical/clinical context or as an exclusionary criterion for insurance coverage. For example, clinical trials might fit a medical definition of the term investigational. At the same time, there might be some disagreement as to whether clinical trials should be excluded from coverage.

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We selected eight definitions of the word investigational. Many of these definitions were adapted from the Blue Cross/Blue Shield's criteria for coverage eligibility, primarily because they have one of the more explicit lists of criteria.

Off-label uses of drugs and devices is the first definition of investigational. Certain practices and certain medical specialties use a large proportion of these drugs. In cancer care, for example, up to 80 percent of the drugs are used off-label when administered in combination regimens and up to 50 percent in single-drug regimens. In pediatrics, up to 70 percent of the drugs are used off-label.

The second definition encompasses National Cancer Institute (NCI) Group C cancer drugs and drugs approved under the FDA treatment investigational new drug (IND). There are those who consider drugs in these two categories as investigational because they do not have final approval from the FDA.

Medical services for which long-term outcomes are as yet unknown was the third definition. For some people, long term is problematic because it implies that a medical service could be considered investigational for many years. For example, the long-term outcome of administering a drug that lowers cholesterol level would be whether patients had a reduced incidence of cardiovascular disease.

The fourth definition was those medical services that have not been evaluated by well-designed, well-controlled clinical trials. This, of course, is a long-standing controversial issue, particularly among oncologists who find it difficult to accept that because a therapy is part of a clinical trial, it is therefore investigational and not eligible for coverage.

Medical services whose beneficial effects have not been shown to be attainable outside an investigational setting was the fifth definition. This, of course, gets into the setting in which care is given. Medical services for which there is no authoritative evidence in the medical community supporting their safety or effectiveness was the sixth definition.

The seventh definition was medical services for which the beneficial effects are outweighed by any harmful effects. This definition essentially involves a risk/benefit analysis. We thought that in patients with a terminal illness, a lower level of evidence of safety and effectiveness might be appropriate when no other treatment options exist.

The last definition was alternative medical therapies not widely recognized by the medical community. This definition would include such therapies as laetrile or immunoaugmentative therapies that are considered to have very little scientific basis.

The panelists were asked to consider these definitions and indicate their level of agreement with them on a scale of 1 to 5, ranging from strongly disagree to agree. The panelists considered each definition in terms of terminal and nonterminal illness and in the two different contexts, medical/clinical and as an exclusionary coverage criterion. Therefore, there were a total of four different evaluations for each definition.

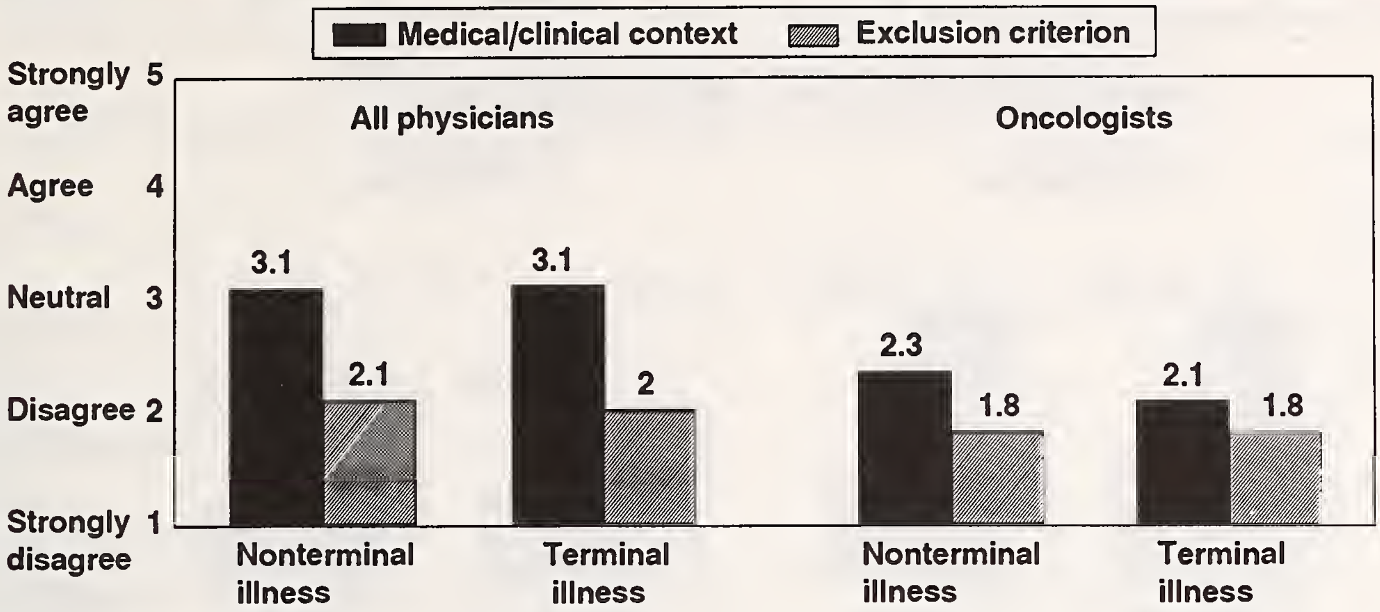
The panelists were selected from our overall panel of some 2,000 physicians who were nominated by medical schools and medical specialty societies. Panelists included oncologists (82), general internists (30), family practitioners (20), obstetricians/gynecologists (30), pediatricians (30), and quality assurance experts (15). We included all the oncologists from our overall panel because we thought this topic would be of particular interest to them. Then we chose a random sample of panelists from specialists. We had a total of 207 panelists; 107 panelists completed the survey for a 52 percent response rate.

The data are presented in Figures 1 through 8. The darker bars represent the interpretation of the definition in a medical/clinical context; the lighter bars represent the interpretation of the definition used as an exclusionary coverage criterion. The two contexts were compared for patients with nonterminal illness and those with terminal illness. We also analyzed the data for all physicians and then analyzed them separately for oncologists.

The y-axis represents the possible survey responses ranging from strongly disagree at 1 to strongly agree at 5. Figure 1 shows the data for the first definition, off-label uses of drugs and devices. The results here are really quite typical of all the definitions we provided. Among panelists as a whole, there was a significant difference between the interpretation of the definition as used in the medical/clinical context versus as an exclusionary criterion for coverage. Quite typically, when the panelists were asked to consider these definitions as exclusionary criteria, the mean responses to the survey were below 3, indicating a level of disagreement. Interestingly enough, there was no significant difference between responses dealing with the contexts involving patients with nonterminal illness and those with terminal illness.

The right-hand side of Figure 1 summarizes the oncologists' responses. Their responses for this definition were similar to those for other definitions: when compared with the responses of the panelists as a whole, their responses for the medical/clinical context were lower, that is, more negative; and, as with the ratings of the group of panelists as a whole, there typically was no significant difference between the ratings for the defini-

Figure 1. Physicians' ratings of the term investigational defined as off-label uses of drugs and devices



tions as used in a medical/clinical context versus as an exclusionary criterion.

Figure 2 summarizes the data from definition 2, NCI Group C drugs and treatment IND. Although there is some agreement that these could be labeled investigational in a medical/clinical context, there was quite a substantial disagreement that this definition should be used as an exclusionary criterion for coverage. The oncologists' 1.7 mean value for the term used as an exclusionary criterion for patients with terminal illnesses was the lowest rating in the entire survey.

Figure 3 summarizes data from the third definition, therapies untested by clinical trials. Again, there is a significant difference in ratings between the two contexts. The rating for the definition as an exclusionary criterion is below 3, indicating some level of disagreement, although this rating is quite close to being neutral.

The same pattern of responses is seen for the fourth definition, therapies confined to investigational settings (Figure 4). As seen in Figure 5, the ratings for the definition, therapies without consensus among physicians, indicate there is some level of agreement that this definition is a reasonable approach to defining investigational therapies.

Ratings for the sixth definition, therapies with unfavorable risk/benefit ratios, and for the seventh definition, therapies with unknown long-term outcomes, are summarized in Figures 6 and 7, respectively. The same general pattern is seen: Among the panelists as a whole, there was a significant difference in the mean rating of the term as used in the designated context with no significant difference in the rating of the definition for patients with or without terminal illness. Although, as seen in Figure 6, the mean rating for the oncologists was similar to that for the panel as a whole, there was no significant difference due to the small number of oncologists.

Figure 8 summarizes the ratings for the last definition, alternative therapies unrecognized by physicians. This is the only instance where there is no significant difference between the mean rating for the definition as used in a medical/clinical context and as an exclusionary coverage criterion. Even among oncologists, there is a higher mean rating for the definition used as an exclusionary criterion.

What conclusions can be drawn from these data? The first is that the panelists did not strongly disagree or strongly agree with any of the definitions. The entire range of means was 3.7 to 1.7, with most clustered around the neutral category.

Among the entire group of panelists and among oncologists, there is no significant difference between the ratings of the definitions as applied to patients with or without terminal illness. This was something of a surprise because we had hypothesized that patients with terminal illness represented a unique subset.

Among the entire group of panelists, there was a significant difference between the ratings for the definitions as used in a medical context and as an exclusionary coverage criterion for all definitions with one exception: alternative therapies unrecognized by the medical community. This definition would include such therapies as laetrile or immunoaugmentative therapy.

The mean rating for the definitions used as an exclusionary criterion for coverage was below 3, indicating

Figure 2. Physicians' ratings of the term investigational defined as National Cancer Institute Group C/treatment investigational new drug

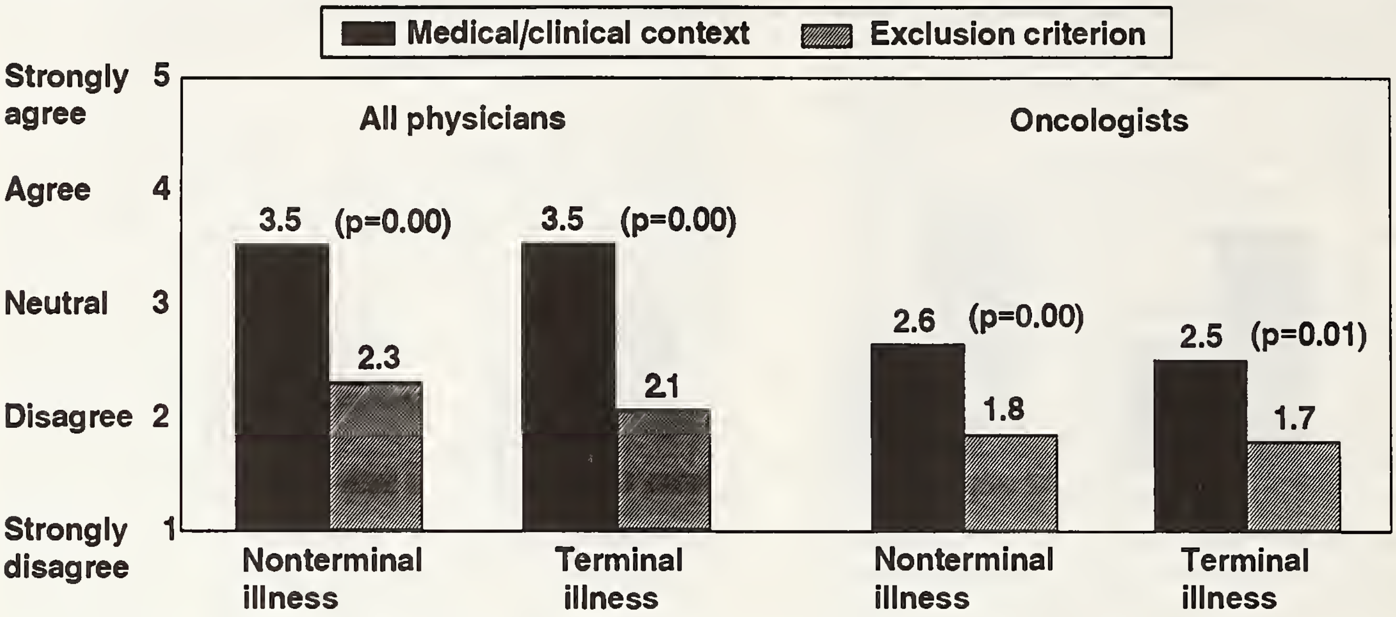


Figure 3. Physicians' ratings of the term investigational defined as therapies untested by clinical trials

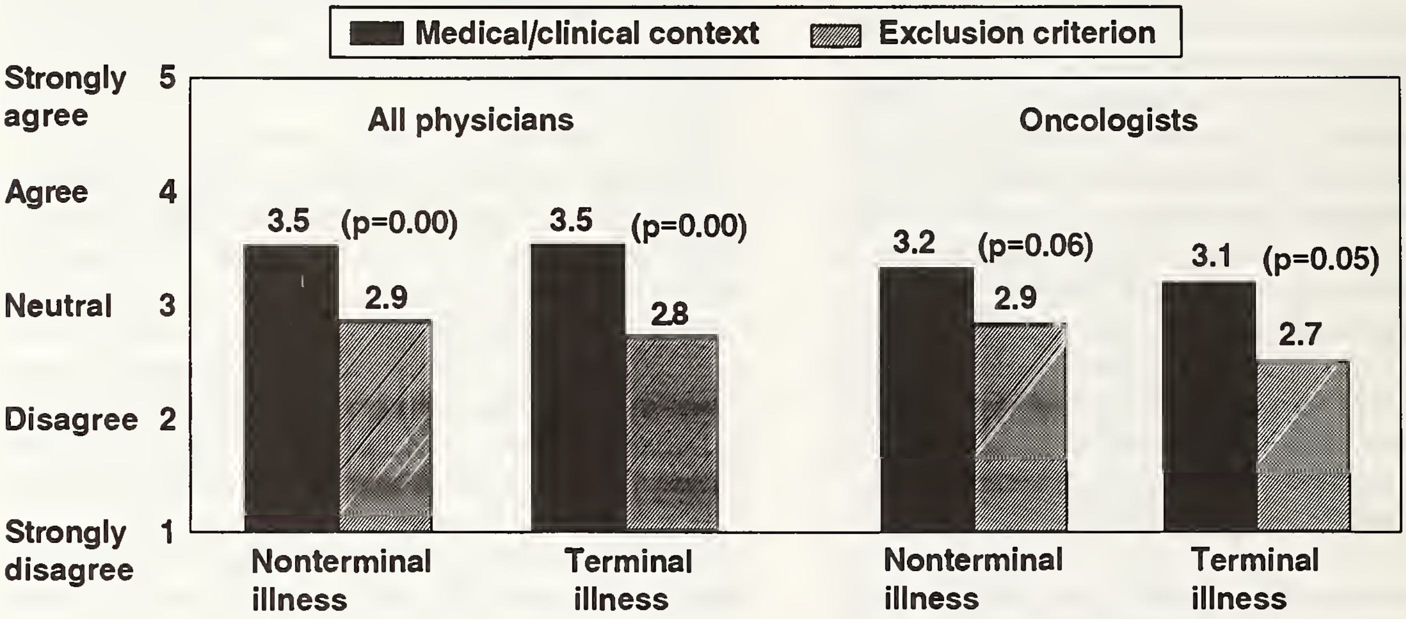


Figure 4. Physicians' ratings of the term investigational defined as therapies confined to investigational settings

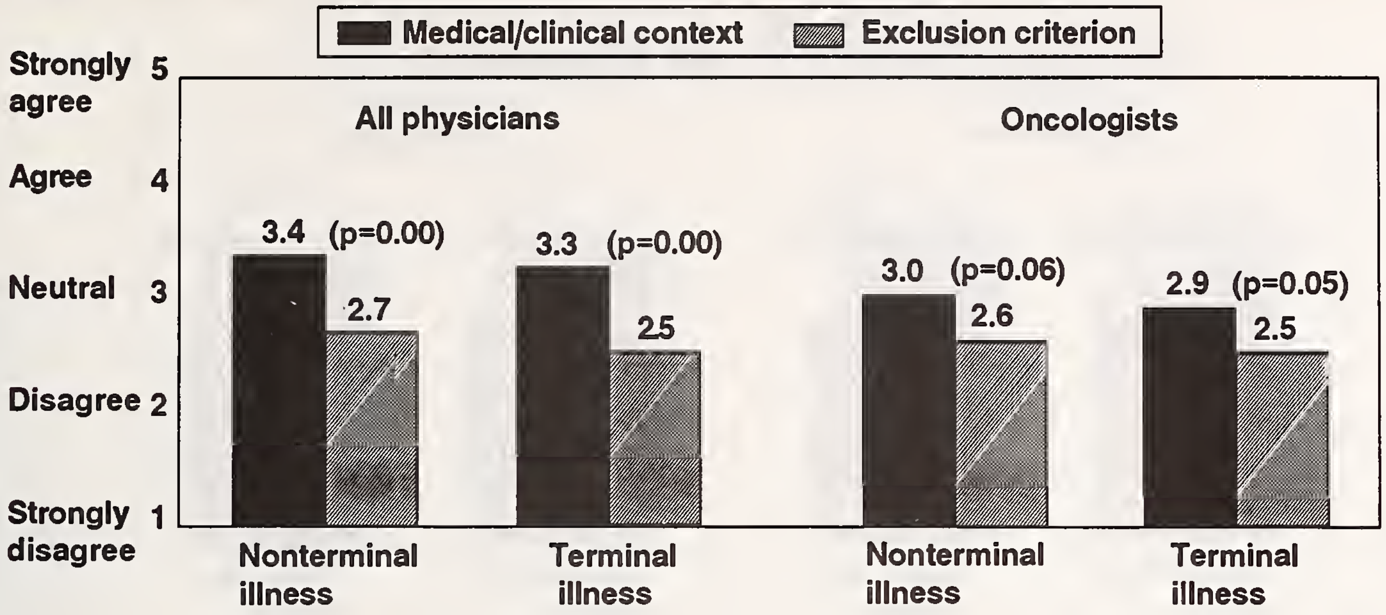


Figure 5. Physicians' ratings of the term investigational defined as therapies without consensus among physicians

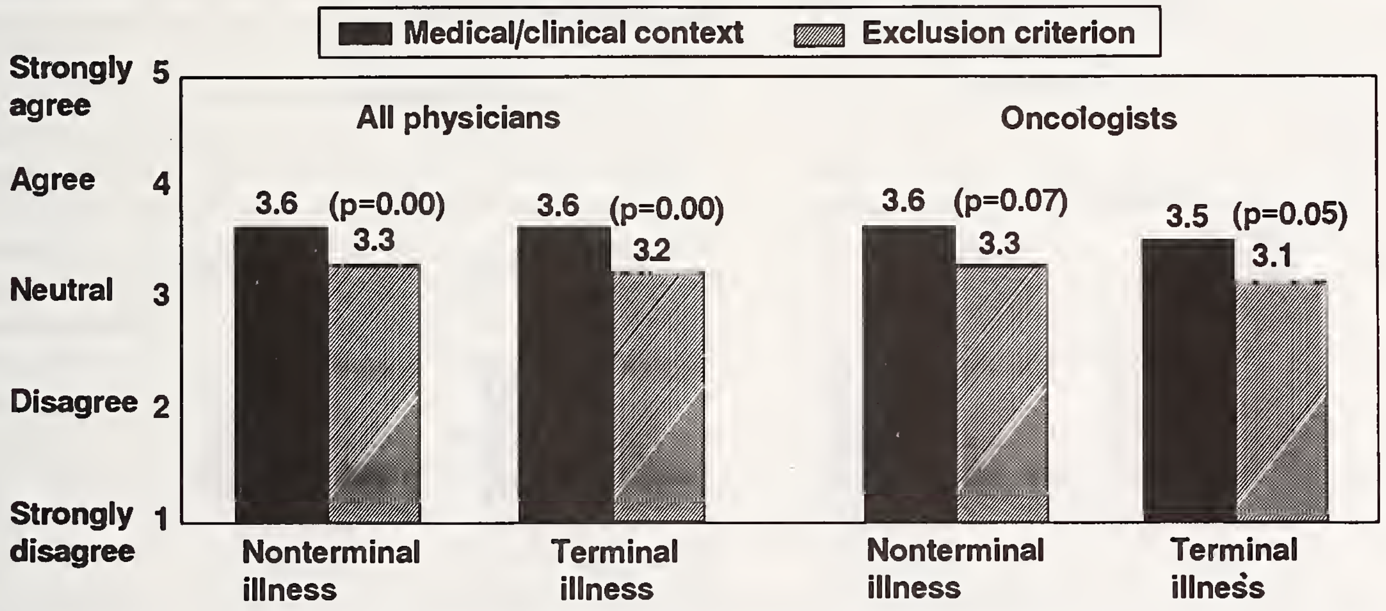


Figure 6. Physicians' ratings of the term investigational defined as therapies with unfavorable risk/benefit ratios

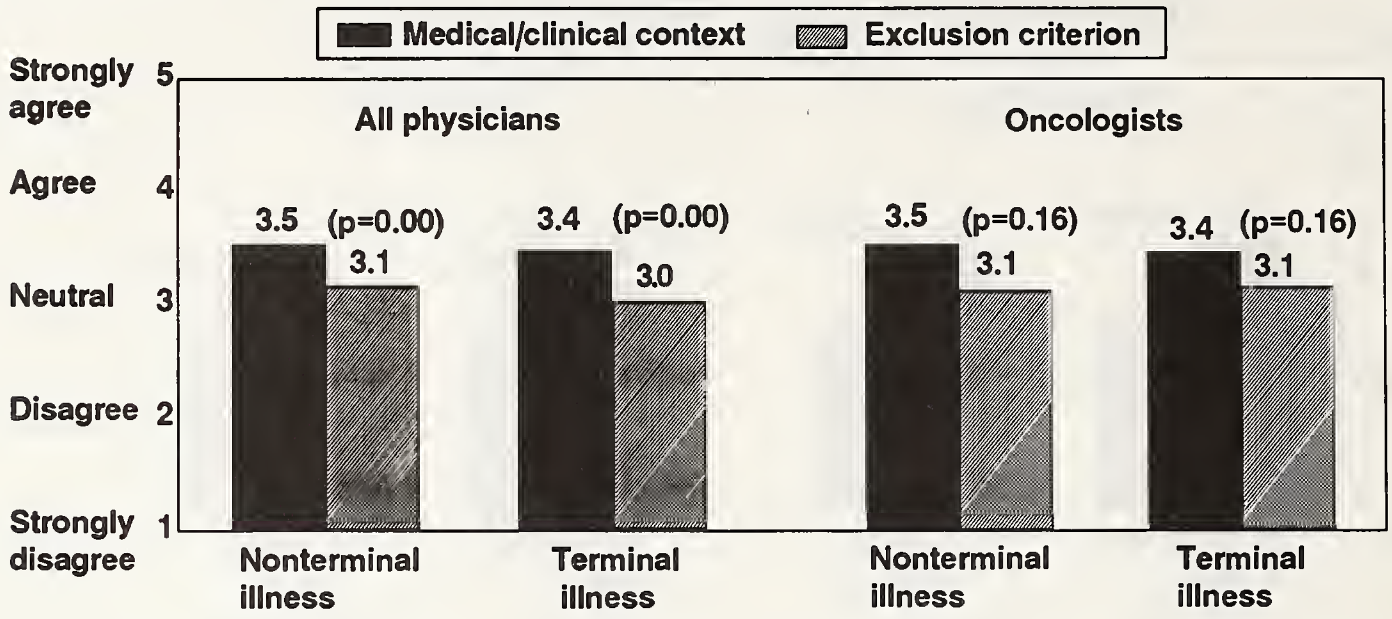


Figure 7. Physicians' ratings of the term investigational defined as therapies with unknown long-term outcomes

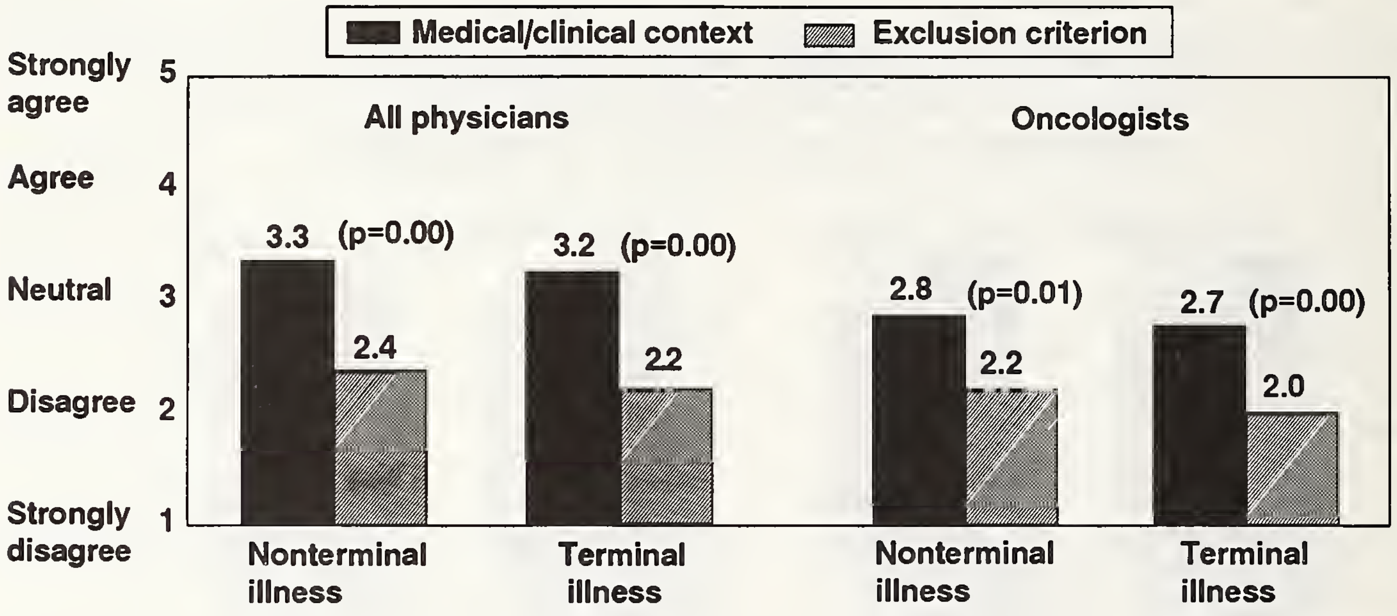
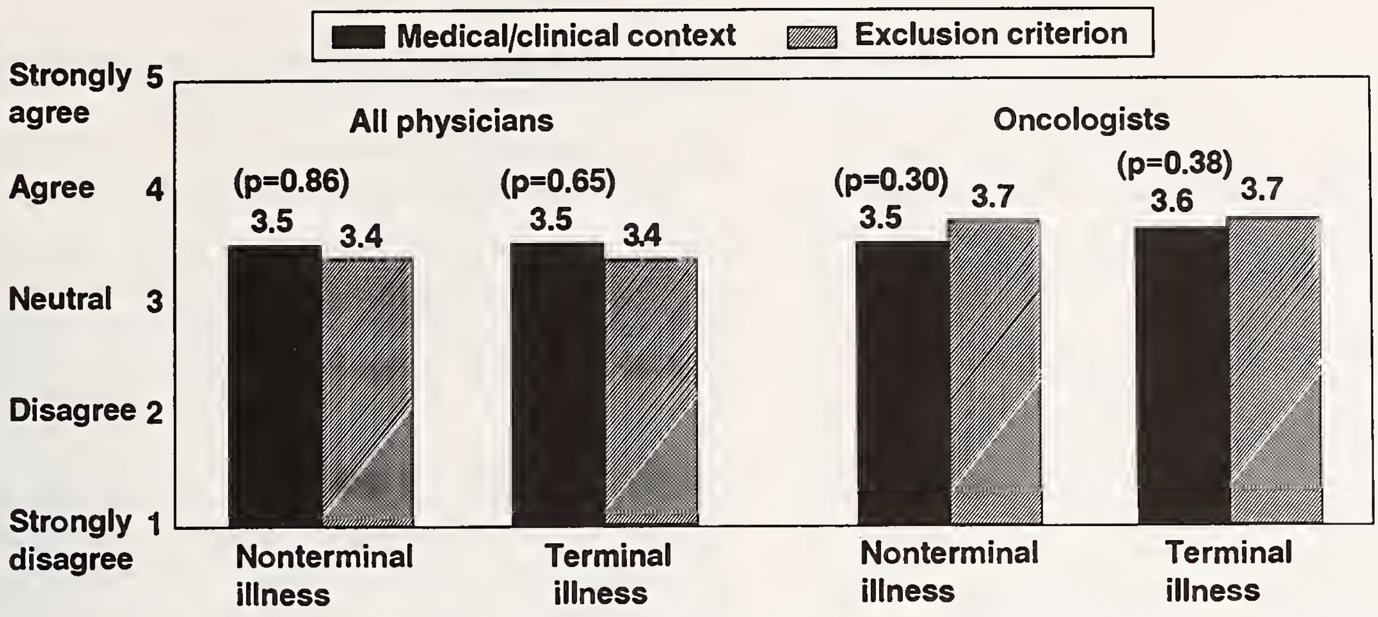


Figure 8. Physicians' ratings of the term investigational defined as alternative therapies unrecognized by physicians



some level of disagreement, in five of the eight cases. The exceptions were medical services in which there is no evidence of a consensus in the medical community, therapies in which the risk/benefit ratio is unfavorable, and those therapies not recognized by the medical community.

Finally, among oncologists, there was a significant difference between the ratings for the definitions as used in the medical context and as used as exclusionary criteria for only two definitions: NCI Cancer Group C and treatment IND and therapies for which the long-term outcome is unknown. The lack of significant differences may be related to the fact that oncologists tended to have a more negative rating of the definition as used in a medical/clinical context.

How do we put this all together and come to any conclusions or recommendations? One might look at the negative ratings of these definitions when used as exclusionary criteria and surmise that physicians are asking for very minimal restrictions on coverage. This is not the case, particularly because of the current economic environment and also because widespread insurance coverage inhibits the ability to conduct the necessary clinical trials. Insurance coverage can be a very important tool in controlling diffusion of new medical technologies in a very constructive way.

Physicians want a coverage decisionmaking process that is consistently applied, reflects the realities of the practice of medicine, and does not rely so heavily on the term investigational. The relationship between payers and practicing physicians has frequently been described as adversarial. There will always be that element of friction primarily because practicing physicians represent individual patients and therefore serve as that patient's advocate, whereas payers must look at the overall population of patients and, from that vantage point, set health coverage policy.

Even so, there is a lot of room for increased collaboration between payers and practitioners. Certainly in terms of coverage policy, there is room for discussions between the two groups to try to refine some of these definitions or to consider ways in which insurance coverage can be used to promote health care and clinical trials to the advantage of both groups.

Discussion/Questions and Answers - Session 2

Q: [Dr. Holohan] I invite the presenters to respond or react to points raised during this discussion.

A: [Dr. Brown] The common theme of all of the presenters in our group is that there really is an opportunity and a need for further collaboration between practicing physicians and payers. This is a fruitful area for collaboration in the future.

A: [Dr. Freeman] I agree. The adversarial issue arises often because whenever we see a patient, we want to do something to help them, such as order a test or procedure. We want to be able to do that test or procedure and for it to be covered; when it is not, we are forcing a patient to pay for something that we are asking them to do. We do not like that, and the situation becomes adversarial. However, in the right spirit and with the right kinds of information gathering, some of these procedures can be paid for during trials; we can all meet on the same ground.

Q: [Kenneth Nelson, Office of the Inspector General, U.S. Department of Health and Human Services] Does investigational therapy raise the total health care costs in this country? Secondly, apparently we have appropriated funds for the National Institutes of Health (NIH) and the agency that is conducting this meeting. We have entitlement programs where everyone pays taxes, whether they want to or not, to support Medicare and Medicaid, and people get health insurance through their employer through a variety of mechanisms. If these funds were to become available to handle what is called investigational approaches, is it likely that the Congress will turn around in a period of deficits and cut the funding for Federal agencies that now provide research funds or that State legislatures will cut the funds for State medical schools and teaching hospitals? Every action may have a reaction in this society. Where do you think this will go if it were to change the current equilibrium?

A: [Dr. Scott] In regard to paying for experimental services, we ought to seriously consider establishing some mechanism to decide what should be tested. In terms of actually paying for it, we have research money from the NIH, and we have money from the drug industry. Also, as Dr. Petersdorf said, other medical care components of the public and private insurers are paying for research. We ought to be explicit, however, about how we address the issue. Now it is simply one case at a time. It is highly contentious and will continue to be contentious unless we can sit down in advance and negotiate how we are to proceed. Otherwise, it will remain a case-by-case issue.

What Congress or the State legislatures will do cannot be predicted. The medical care industry has grown in the face of economic downturns and everything else. It is the greatest growth industry in the country right now, and it has considerable momentum to continue to grow.

A: [Dr. Brown] I agree with Dr. Scott that we need to be more explicit about how we make decisions as to which experimental therapies should be covered. Physicians would like consistency. It is very difficult for them to understand why, when you are looking at two arms of a clinical trial and the so-called conventional arm has not been studied in a formal way, it is considered the conventional arm. Then there is the so-called experimental or investigational arm, and it is seemingly an arbitrary decision as to what is considered investigational and thus not covered. So, there is much to be gained by trying to figure out ways in which third-party payers and providers can structure clinical trials to the betterment of both and provide the kind of data that everyone needs.

Q: [Dr. Holohan] We have talked about a "task force" composed of people with somewhat different viewpoints—clinicians, probably clinical researchers, and payers—to provide early evaluation and identification of the kind of innovations we are discussing. Would anyone like to be a little more specific in terms of designing this group? Who specifically should it include?

A: [Dr. Scott] You clearly want scientific and clinical expertise and experience; you want those who pay the bills and some good public representatives who can appreciate and come to understand the complexities that must be addressed. The public members can then be your greatest advocates for a solution.

A: [Dr. Ferguson] It has to be a public/private group; that is, some ambience of impartiality is needed in this sort of a group.

A: [Dr. Holohan] Or at least balanced partiality.

A: [Dr. Ferguson] Balanced partiality perhaps. Industry, the drug industry, health manufacturers, and so on should be involved, and that is a little tricky. They obviously do not want to disclose trade secrets and the like, yet they also are involved in some new things. An independent group can spot new things around the world through the medical literature, advertisements, or some other mechanism; we would need that kind of input, and it is not easy to get in the competitive financial world.

Q: [Max Boller, MedCenters Health Plan, Minneapolis] To ask a followup question, we have sat through a number of meetings like this over the past couple of years, and everybody asks interesting questions. Everybody seems to be doing a good job and working hard, but the solution always seems to lie someplace else. The issue is, as Dr. Scott raised in his summary, how to identify a national board and what its composition should be. Who has the responsibility to put this together? What will be the responsibility of the board once it is assembled? And what authority would it have?

A: [Dr. Scott] Those are excellent questions, and they should be an explicit part of the discussion of health care reform. This is an issue in terms of financing mechanisms and one with which we should come to grips. For instance, the American College of Physicians is now working its way through a set of proposals and questions about what the nature of the reform might appropriately be. It is certainly part of our job to propose how this group ought to be constituted, its governance, its financing, and so on. Other groups represented here who think this is a good idea should put their ideas on the table. The sponsor of this conference—the Agency for Health Care Policy and Research—might want to go forward and get us into more specific policy considerations rather than this kind of forum. This is the think tank without any formal recommendations.

A: [Dr. Ferguson] I believe the question asked was about who should put this group together.

Q: [Mr. Boller] Yes, that is part of it. What is the authority and the responsibility of this group? If we leave it to our medical colleges, they may get it done. The NIH is using all of its allocated money to do things that are purposeful and wonderful. So, where does this bold new venture get its pump priming?

A: [Dr. Ferguson] I do not know that I can speak for the NIH on this, but I feel that the Government has a responsibility for the health of its citizens. Therefore, I think that the combined interests of all the various groups that might be represented can best be convened by a Government entity —that is, they would host it much as this meeting is being hosted. All sides should be represented, and that is a responsibility of the Government. Although this raises the question of national health coverage and all that entails, it still is an important point.

A: [Dr. Holohan] Insurance companies paid for extracranial, intracranial bypass for 20 years; it costs a significant amount of money. The NIH spent $9 million, 20 some odd years after the procedure was first described, to do the only prospective randomized trial which, despite the arguments in some parts of the neurosurgical community, rather conclusively proved that the technology was ineffective in preventing stroke. One could argue that if this had been done initially, 20 years of reimbursement would have more than compensated for the cost of the trial.

Q: [Robert Pendergrass, National Heritage Insurance, Austin, Texas] Dr. Ferguson, I really do not disagree with any of your comments, but I think that the pluralistic approach to financing well-controlled trials to determine feasibility of new techniques and new technologies has to be borne by the Federal Government. There should be a mechanism through Congress for all of the citizens of the United States to participate. The burden should not be on isolated segments of society.

In the drug field, it is reasonable for the pharmaceutical manufacturers who want to develop new drugs and to push those new drugs to physicians for their use to pick up the entire cost for the development as well as the clinical trial testing.

There are the institutions that pride themselves on being research institutions and look for funding for their research from sources other than their endowments or from a collaborative effort with the NIH in order to carry out well-controlled protocols. I submit that physicians are advocates of their patients only to the point where they find out patients do not have third-party coverage. At that point, they lose interest in the treatments that they had demanded you pay for. I believe the AMA needs to work more realistically with its physicians to come up with a greater consensus than a neutrality on what is acceptable and what is not acceptable.

A: [Dr. Brown] I agree that the definitions as given here, at least from a medical/clinical context, all showed neutrality. That may be due in part to the pejorative sense that the word investigational has acquired because it is often equated with coverage denial. To a certain extent, state-of-the-art is used as a substitute for investigational in those instances and it has a more positive connotation.

I am not sure how to solve the dilemma you cited. When we talk about providing or trying to generate clinical trials and information early on in the evolution of a new technology, certainly physicians should bear part of this burden in that at least physician innovators should be encouraged to, or actually responsible for, trying to generate the clinical trials that are needed by actively pursuing the funding to conduct the trials.

When a technology diffuses too rapidly and there is widespread insurance coverage, the opportunities for clinical trials no longer exist, and that is a problem; we have to get clinical trials going early, and for that, physicians are partially responsible.

A: [Dr. Pendergrass] Availability of funds today is the greatest determinant of rationing. We are all concerned about the experiment that Oregon has begun, but they are only doing openly what we do now. Physicians are the greatest rationers of health care based on the availability of reimbursement. That needs to be changed in some way. So inevitably the number one question is to define the rational amount of health care to which every citizen in the United States is entitled and then to determine how we are going to add into the system those technologies that evolve; I am not an advocate of stopping technological development.

A: [Mr. Stein] At these conferences, you always hear who should pay—the employers, the Federal Government, the State governments. Really, the burden is shared by all those sectors now, and all those sectors are suffering from what most people would acknowledge is a lot of inappropriate care—inappropriate because we do not know what is effective.

The more we can do of the kinds of research that the agency is sponsoring, the sooner we will be able to get better value for what we spend. We all have a stake—no matter where the funding comes from—in designing and coming up with the protocols and studies that can lead us to a more effective set of services.

This whole enterprise is very, very small and embryonic; if we can make it more robust, much can be saved. Employers will save, the Federal Government will save, and State governments will save.

Q: [Dr. Holohan] I note that most of the responses to the AMA questionnaire tended toward neutrality, but I was surprised that there was very little difference in the rating categories of services not evaluated by well-designed, well-controlled clinical trials. In the general agreement of the medical community, they appeared to be viewed as equally informative.

A: [Dr. Brown] Compared with what?

A: [Dr. Holohan] In terms of their use as a criterion for evaluating whether something was experimental. A general belief of the medical community apparently was considered to be as useful in determining whether something was investigational as the presence of evidence based on adequate and well-controlled trials.

A: [Dr. Brown] We did not ask the panelists about usefulness. We asked them if they agreed that this is an appropriate definition of the word investigational. A separate question that we could have asked our panelists concerns the usefulness of the definition. Also, we could have asked: Do you think that clinical trials should be used as an exclusionary criterion for coverage? We might have gotten different answers.

Q: [Dr. Ferguson] At a New York Life symposium, we learned that insurers are faced with and must make decisions instantaneously about reimbursement; they sometimes try to resolve problems with telephone conversations.

I understand, because of my court experiences, the conundrum. You are not likely to win in these court cases for a number of reasons; but we need to make a rational decision for reimbursement rather than make the decision on the phone or because we know of a tuberculosis patient or somebody with acquired immunodeficiency syndrome sitting in Congress. I realize the media puts a big burden on you to do these things.

A: [Dr. Cova] I think you are implying that the private insurance industry is unwilling to cooperate. We are not averse to helping. We are trying to help, and we want to help you define how we should help. We do not feel that it should be our responsibility entirely. Reimbursement for everything that is experimental is not the answer because the system will collapse.

A: [Dr. Ferguson] I agree, and I think the process that the Health Insurance Association of America has initiated will help tremendously.

A: [Dr. Cova] We have undertaken some technology assessment activities ourselves, and we provide those assessments to the public. They are public documents. It is foolhardy for us as a society, however, to think these insurers have access to an infinite source of money and all you need to do is get them to reimburse for these things and everyone will live happily ever after. They won't. The system will collapse.

Food and Drug Administration Perspective

Peter Rheinstein, M.D., J.D.

My first introduction to the question of experimental versus state-of-the-art came shortly after I joined the Food and Drug Administration (FDA) in 1974. Calls would come in from insurance companies all over the country. The caller would ask if "the treatment of disease X is an approved indication for drug Y?" As the Director of the Division of Drug Advertising, I knew that the package insert contained the approved indications for which a company could advertise. After checking a copy of the insert, I would reply that disease X was not an approved indication for drug Y. The caller's next question would then be, "Then you would say that the use of drug X is experimental for the treatment of disease Y?" I would respond affirmatively, and the caller would thank me and say goodbye. It was not until several years later that I learned that my answer justified the cost of the insurer's long distance call because my naive agreement that a particular use was experimental served as the basis for the denial of a patient's claim.

In fact, as my experience as a private practitioner should have told me, the FDA's regulatory determination of what is an approved treatment is a giant step from what an individual physician determines is reasonable and necessary to the treatment of his or her patient. The dilemma may exist as a patient's need for an unlabeled use of an approved product or as a patient's need for an unapproved product. Sometimes the patient's condition may be so critical that without a new therapy he or she will not survive until accumulation of safety and efficacy data sufficient for the FDA to make a definitive judgment.

The dilemma may be expressed best by the FDA's treatment investigational new drug (IND) program where the drug or biological—although legally investigational—is viewed as standard therapy by the medical community and, indeed, even by the FDA when it publicizes the product's availability through press releases, speeches, and announcements in medical journals. The FDA perspective fulfills important statutory mandates that came in response to real societal problems. The controlled clinical trial has allowed society to embrace therapies that work and ultimately to discard those that do not.

Figure 1 shows some important milestones in the development of the Federal Food Drug and Cosmetic Act. The 1906 law was passed after Upton Sinclair exposed unhealthy practices in the meat packing industry. It came at a time when known deleterious substances were frequently packaged with new and fanciful names. The 1906 law provided that a drug product must be accurately labeled as to its ingredients.

In 1938 a law came after a drug manufacturer used ethylene glycol to make a liquid formulation of sulfanilamide. The law required that, in addition to having an accurate list of ingredients, it had to be shown that a drug was safe prior to marketing.

The 1962 law was passed after samples of thalidomide distributed prior to commercial marketing caused deformities in children born to mothers who had taken the product during pregnancy. That law came after hearings which showed that most doctors in their own practices did not see enough patients to make a statistically valid determination about the effectiveness of a particular drug in the treatment of a specific indication. The 1962 law required that a drug had to demonstrate substantial evidence of effectiveness prior to marketing.

The 1962 amendments defined "substantial evidence of effectiveness" to be evidence consisting of adequate and well-controlled investigations including clinical investigations by qualified scientific experts that prove the drug will have the effect claimed by the labeling.

The FDA classifies adequate and well-controlled studies into five groups in descending order of preference. Our first preference is for placebo-controlled concurrent clinical trials; the second for dose-comparison concurrent; the third for no-treatment concurrent; the fourth for active-treatment concurrent; and finally, for historical controls, either implicit or explicit.

Dr. Rheinstein is Director, Medicine Staff, Office of Health Affairs, Food and Drug Administration.

Figure 1. Development of the Food, Drug, and Cosmetic Act

Prior to 1906 -	No effective regulation of human drugs
1906 -	FDA could remove a drug from the market only if FDA could prove the drug was adulterated or misbranded
1938 -	Manufacturer had to provide FDA evidence of of "new drugs" before marketing
1962 -	Manufacturer had to provide evidence of effectiveness in addition to safety before marketing

Key: FDA = Food and Drug Administration

In 1976, Congress passed a law establishing a class of devices for which FDA must determine safety and efficacy prior to marketing. These are devices for which there is insufficient information to determine that the general controls are sufficient to assure safety and effectiveness or to establish performance standards. Also included are devices that are life supporting or life sustaining, devices that are intended for a use that is of substantial importance in preventing impairment of human health, or devices that present a potential unreasonable risk of illness or injury.

With most devices, it is difficult or impossible for a clinical investigator to do a blind trial. In a blind trial, the investigator does not know whether the patient has received the investigational product. For devices, then, valid scientific evidence in order of preference includes well-controlled trials, partially controlled studies, studies and objective trials without controls, well-documented case histories, and significant human experience with a marketed device. These last two categories of evidence represent a standard broader than that permitted for evidence of the effectiveness of drugs. Valid scientific evidence for the effectiveness of devices specifically does not include things like isolated case reports, random experience, unsubstantiated opinions, and reports lacking sufficient details to permit scientific evaluation.

The 1976 law provided for the continued marketing of devices already on the market at that time. It also provided a mechanism to allow marketing of devices found to be substantially equivalent to other devices that had been on the market prior to 1976. A finding of substantial equivalence does not specifically require proof of safety and effectiveness. The 1976 law went on to provide a mechanism for FDA to call for applications for premarket approval (PMA) of pre-1976 devices including products found to be substantially equivalent to other pre-1976 devices.

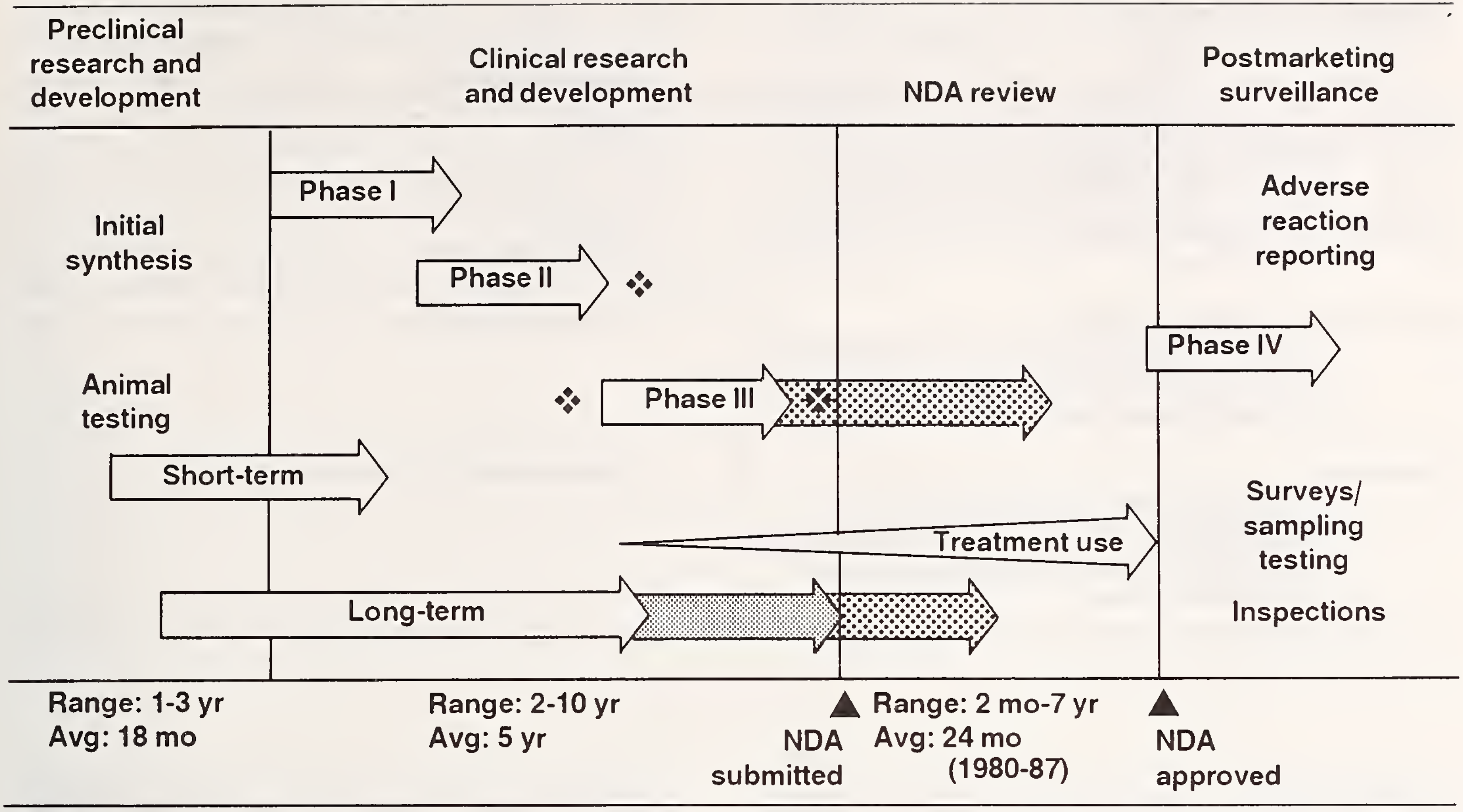
This happened, for example, in the case of replacement heart valves. Of course, these valves are now, and were at the time the FDA called for the applications, standard medical therapy; but at least one possible regulatory route would have termed these valves investigational during the preparation of PMA applications. If an FDA status of investigational had been interpreted as meaning the same as experimental, this could have resulted in patients' being denied reimbursement for what was, in fact, standard medical therapy.

The Food, Drug, and Cosmetic Act does not generally restrict the manner in which a physician may use an approved drug. In the FDA drug bulletin for April 1982, the FDA said very specifically that unapproved or unlabeled uses of approved drugs may be appropriate and reasonable in certain circumstances and may even represent important approaches to drug therapy which have been extensively reported in the medical literature. Such uses range from salutary to hazardous and encompass medical practice situations ranging from infrequent to widespread. In oncologic and antiviral therapies, the need for new treatments means that much use has not achieved the status of approved labeling. The difficulties in carrying out trials on children mean that products for many different uses are approved without the data required to approve pediatric labeling.

The package insert for an approved product is the result of negotiations between FDA and the sponsor and constitutes important information for the health care professional. It is essentially a precis of the information that FDA and the sponsor agree has been demonstrated by the evidence submitted to FDA by the sponsor. The sponsor may not promote the product for indications that do not appear in the insert, and the promotional materials must also reflect all the safety considerations in the insert. Obtaining that license to promote a product for a particular indication is a fundamental incentive for the sponsor to fund research to support approval for a new indication.

Figure 2 illustrates the FDA product approval process and shows the drug development process for a new chemical entity. The process is divided into four stages:

Figure 2. New drug development



❖ Sponsor/Food and Drug Administration meetings encouraged
Key: NDA = New drug application.

preclinical research and development, clinical research and development, new drug application (NDA) review, and finally postmarketing surveillance.

Preclinical research and development including initial synthesis and animal testing takes 1-3 years, with an average of about 1.5 years. Clinical research and development consists of three phases. Phase I, clinical pharmacology studies, is primarily to establish safety and proper dose level for human trials (Figure 3). Usually 1-10 but occasionally as many as 50 volunteers are studied. Phase II, small-scale controlled studies, uses 50-200 patients with the disease or condition. The primary purpose is an initial determination of efficacy. Phase III consists of both controlled and open trials on up to 1,000 or more additional patients to make a definitive determination of safety and efficacy. From the time the drug is first introduced into humans until an NDA is filed takes about 2-10 years, with an average of 5 years. This period is a bit shorter for anti-infective drugs because the effect of the drug is apparent after a short time. The period can be longer for psychoactive drugs and antiarthritics because these drugs treat diseases which go through natural ups and downs. These ups and downs must be distinguished from the effects of therapy.

The period of clinical research and development is repeated for new uses. Knowledge such as the proper dose, transferrable from studies on other uses, may shorten that process somewhat. During clinical trials, a new product may show promise for individual patients whose disease could not otherwise be adequately treated. For example, small-scale trials with azidothymidine produced such a dramatic drop in the death rate from acquired immunodeficiency syndrome that the drug was approved on the basis of those trials.

More often, new therapies may produce improvements that suggest their use is reasonable and necessary for some patients, but these improvements may not be so striking as to eliminate the need for further studies for marketing approval. The treatment IND is a mechanism adopted by the FDA that allows sponsors to get such drug products to the patients who need them.

Finally, in new drug development, the period of NDA review takes from 2 months to 7 years with an average of about 24 months for all NDAs and 30 months for new

Figure 3. Clinical studies

Type		Primary purpose
Phase I -	clinical pharmacology studies — usually 1-10 male volunteers (can be as many as 50)	Safety
Phase II -	controlled studies in patients with disease or condition — 50-200 patients	Efficacy
Phase III -	both controlled and open trials— up to 1,000 or more additional patients closely monitored by sponsor for adverse reactions and information to be used for setting dosage requirements and labeling	Safety and efficacy
Treatment use	Involves patients with a serious, life-threatening, or terminal illness when alternative treatment is not available or not effective and proposed treatment use has some evidence of effectiveness	Treatment of individual patients

chemical entities. A prioritization system allows applications for products representing major therapeutic gains to be reviewed more quickly. Both clinical trials and long-term animal studies may continue through the period of NDA review.

Phase IV studies are done after a product is already on the market. During this time, the FDA is receiving reports of experience with the product. Based on these reports, the FDA may seek to alter conditions of marketing.

Earlier, I stated that the treatment IND is the best example of the dilemma between therapy defined by FDA as investigational but recognized by the medical community as state-of-the-art. The circumstances that permit a treatment IND are quite specific: the drug is one intended to treat serious or life-threatening disease; there is no comparable or satisfactory alternative drug or therapy to treat that stage of the disease in the intended population; the drug is under investigation in a controlled clinical trial or all of the trials have been completed; the sponsor of the drug is actively pursuing marketing approval with due diligence; and finally, a reasonable body of scientific data exists and indicates that the agent may be effective and that it has an acceptable degree of toxicity.

The Medicare staff in the Office of Health Affairs is FDA's liaison with the Agency for Health Care Policy and Research (AHCPR) Office of Health Technology Assessment. In fact, OHTA's director, Dr. Holohan, directed FDA's Office of Health Affairs before transferring to AHCPR.

I still receive calls from insurance companies. Whether the FDA can provide useful information depends on a number of factors. Publicly available information on unlabeled uses and unapproved products includes information disclosed during an open session of an advisory committee. If there has been no such advisory committee meeting on the information or the data were discussed in a closed session of the meeting or if such data were submitted as a part of an NDA or PMA but otherwise not made available by the sponsor, the FDA cannot release the data. Others must then rely on information in the published medical literature or other information the sponsor makes available.

Most importantly, if data were submitted to the FDA as part of a supplemental application and the FDA actually turned down that application based on safety or efficacy or any other grounds, such information may not be releasable by the FDA. Thus, at the same time, if a study is published in the medical literature stating that a new indication is effective, the FDA may have actually looked at that data and rejected them on safety or efficacy grounds. This might have been determined on the basis of the same data, or the FDA might have arrived at such an opinion based on additional data available to the agency but not submitted for publication; or the FDA may have audited the study and found it unreliable or deficient in various ways.

In conclusion, no one wants to pay for a drug or device that has failed to beat the placebo in a controlled clinical trial. The FDA approval process has a major role to play in establishing those therapies which work and sifting out those which do not. For a particular patient, a therapy may be reasonable and necessary before it is FDA approved. Where therapies are reimbursed prior to final FDA approval, sufficient incentives must be maintained for the sponsor to generate the necessary data to make a final determination on safety and efficacy. Once a therapy is approved, it is for others, not particularly FDA, to look at questions of relative efficacy, appropriateness, costs, societal values, and other factors in deciding about reimbursement and coverage.

When the insurance company calls to ask if product X is an approved treatment for disease Y, I may still say no and it may be investigational, but I add that it may be reasonable and necessary, even state-of-the-art for a particular patient. I offer what help I can, but the decision on coverage and reimbursement is ultimately not exactly the same as FDA's final determination of safety and efficacy.

Manufacturer's Perspective

Gerald Messerschmidt, M.D.

Eighty-five years ago, the Congress was concerned about the relative question of experimental versus state-of-the-art care and created through a Congressional act the predecessor to today's Food and Drug Administration (FDA). Now, 85 years later, the pharmaceutical industry and the FDA are still discussing the question of experimental versus state-of-the-art.

My recommendation is that we develop a standard methodology to assess all the data, not just a small segment, but all the data that are available in relationship to therapies and procedures and other medical interventions so that we can make a rational determination for approval, marketing, and eventual reimbursement of these therapies.

Why are we attending this conference? In my opinion, cost is the major impetus. The rising cost of health care is extraordinary. It has grown at 10-20 percent per year over the last several years and is expected to be over $1.5 trillion in the year 2000. As mentioned by an earlier speaker, 12 percent of our gross national product this year for health care is an extremely high figure.

The pharmaceutical industry represents only about 8 percent of national health care expenditures. If pharmaceutical costs were eliminated entirely from the cost of health care, it would not eliminate even the rise in inflation. Many variables are involved in the rising costs of health care. One suggestion is that procedures may not be used appropriately; they may cost a great deal and subsequently not benefit the patients. In a study conducted in the middle 1980s, 20-30 percent of therapies were found not to be justifiable, or it was debatable whether they were of benefit to patients when they were applied.

The pharmaceutical industry is regulated by the FDA. As demonstrated in Figure 1, we have a preclinical and a clinical timeframe (a time for putting together the data for submission to the FDA); then there is the timeframe for submission to the FDA and FDA approval, with an average time for approval for drugs of about 30-32 months; and finally, many trials are conducted after approval. The FDA regulates every step of the way in this process. In the preclinical area, good laboratory practice (GLP) is the name of the regulation applied. In the clinical area, good clinical practice (GCP) is the name of the regulation that defines every step of our process, and in the area concerned with the manufacturing of the product, good manufacturing practice (GMP). We are regulated in the marketing of the drug after approval, not only by the FDA, but by the Federal Trade Commission (FTC) and the Interstate Commerce Commission (ICC) as well.

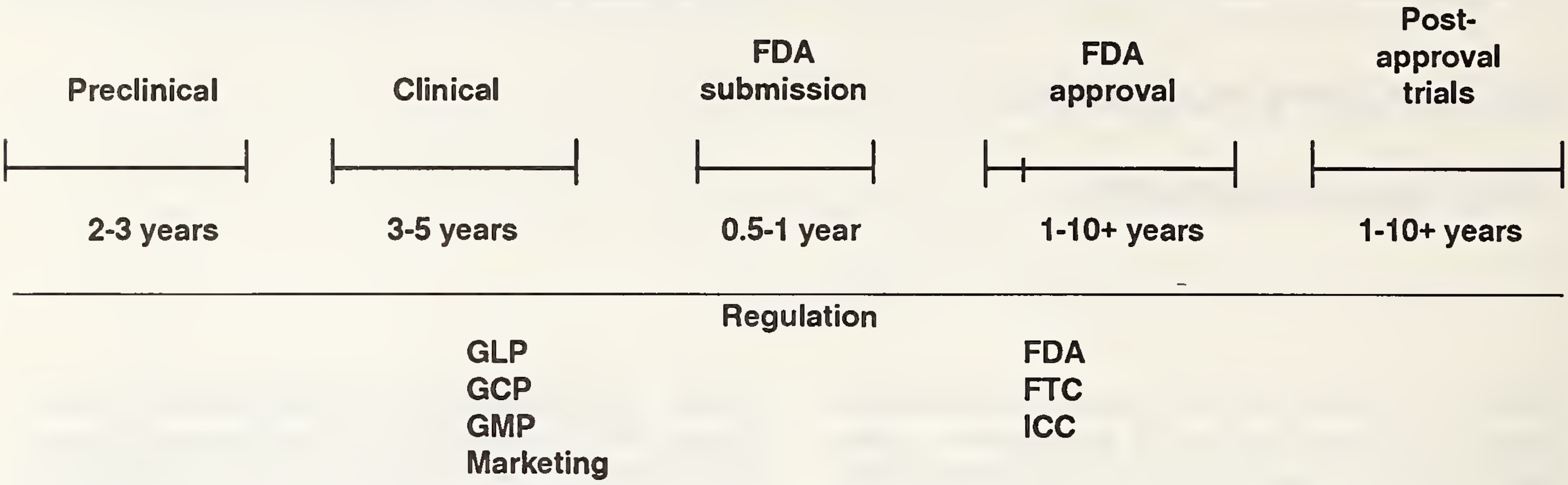
How does this relate to the question we are addressing at this conference? That is, what is experimental and what is state-of-the-art care? The process of pharmaceutical development is outlined in Figure 2: preclinical studies, clinical studies which may last many years, time needed to put the FDA submission together, and finally FDA approval.

By FDA regulation, a new chemical entity is considered experimental until it is approved. If we look at this carefully, however, FDA approval is largely dependent on data generated many months to many years previously. Often, much of this information is available outside of the FDA; it is published in the medical literature and available to practitioners. They may take those data and define the third line in the figure to be the length of the experimental time of the therapy. Because of this type of discrepancy—between the FDA's definition of experimental and the practitioner's definition of experimental—many patient activist groups and the FDA define this time as the parallel track and time for the treatment investigational new drug process (commonly referred to as a treatment IND).

This occurs during the first approval of the drug. What about in subsequent uses of products? In Figure 3, again depicting preclinical, clinical, FDA submission, and approval, the same diagram now gets a little more complicated. The FDA considers for the first indication that the experimental time will end at the time of approval. The physicians, however, may have the data at an earlier time and may define experimental as ending soon after the clinical trial data are known.

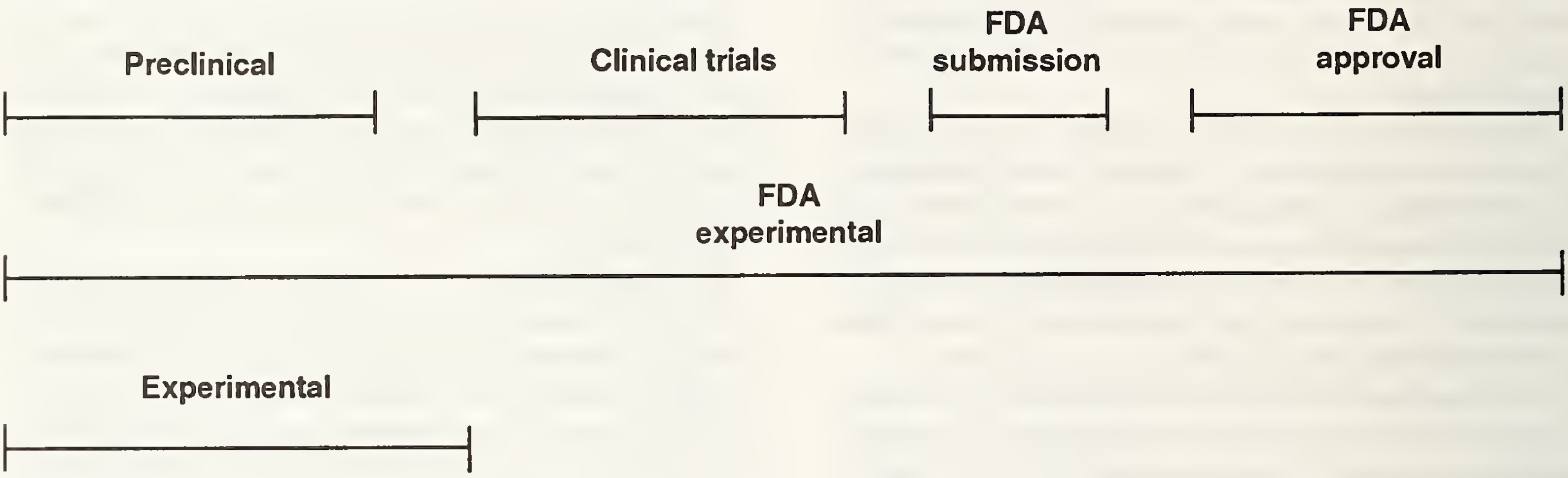
Dr. Messerschmidt is Executive Director, Medical Affairs, CIBA-GEIGY Corporation.

Figure 1. Regulation of pharmaceutical development



Key: FDA = Food and Drug Administration; FTC = Federal Trade Commission; GCP = Good clinical practice; GLP = Good laboratory practice; GMP = Good manufacturing practice; ICC = Interstate Commerce Commission.

Figure 2. Process of pharmaceutical development



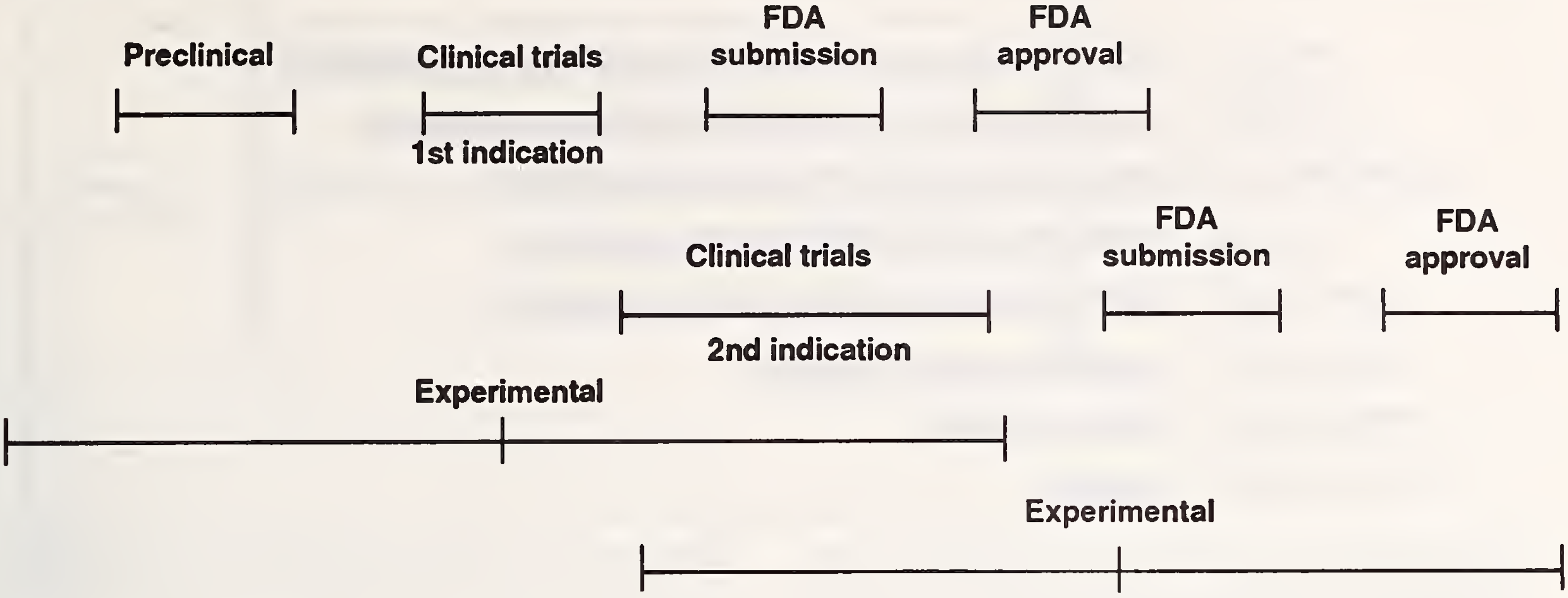
Key: FDA = Food and Drug Administration.

If this happened to be an anticancer drug, however, the first indication might be for treating one type of tumor, and it might be discovered subsequently that a second type of tumor could possibly be treated by the same drug. The trials for the second use might begin prior to drug approval and perhaps even end before the first indication is approved by the FDA; however, the FDA process still goes on for the second indication, with the putting together of data for submission and approval.

For this second indication, the FDA considers a drug experimental until the time of approval of the second indication. As I mentioned, however, the drug will be marketed prior to this second approval, and the physician then has the ability to use the product in his or her best judgment based on the data. So, there is again a dichotomy between the FDA's definition of what is experimental and the practicing physician's definition of what is experimental.

This has led some people to suggest that the FDA's definition of experimental is narrow; why can we say that? First, it may be that practitioners acquire knowledge and have the ability to put the knowledge into practice faster than the FDA in many circumstances. The FDA also is restricted in many ways, since the data it can use in the approval process are regulated by the Code of Federal Regulations. Many good studies that are performed by well-known individuals or institutions cannot be used in an FDA approval process. Of course, there are other factors. We are all aware that the work load at the FDA is quite heavy and has an impact on the approval process.

Figure 3. Process of pharmaceutical development for subsequent uses of products



Key: FDA = Food and Drug Administration.

Is there a way that we can all look at the data and come to a conclusion in a more objective and more reproducible fashion? About a year and a half ago, a conference was held in Ann Arbor, Michigan, to discuss this question. To summarize the deliberations of the Ann Arbor Conference Defining Multiple Levels of Medical Care, it was agreed that the literature is a standard source that is available to everyone; the literature does have study design variations in the data, but these variations are quantifiable. The quality of these studies also varies, but the variations can be quantified. This can be done for individual studies, and the accumulated literature can then be assessed. How can we find an easy way to quantify the study design? At the Ann Arbor conference, the participants were only asked to rank the study designs, and this ranking is shown in Figure 4. As you can see, the long-term and randomized studies had the highest rank, whereas the nonrandomized and non-peer-reviewed studies had the lowest rank. This can be used to plot these studies.

The Ann Arbor conference came up with the plot shown in Figure 5. First, the study design quantification is on the "x" axis and quality on the "y" axis. The study design quantification is divided into negative and positive results. The next question concerns the type of study conducted. Was it non-peer-reviewed or nonrandomized? A long-term study of high quality with a positive result would be marked in one place, whereas a long-term study, also of high quality but with negative results, would be marked in a different place.

An example of this technique used in an everyday situation is the use of estrogen replacement therapy in postmenopausal women with a uterus. Clearly, the evidence is very strong that estrogen alone in this population leads to an increase in uterine cancer. The data are equally strong that the addition of a progestin abrogates this increase in uterine cancer.

How would this look on an Ann Arbor plot? Figure 6 is the same plot with a study design quantification on the quality axis. The small dots are diagrammatic and represent the individual studies of varying design and varying quality, and the large dot outlines the accumulated literature in one representation.

A second example might be the drug encainide. Encainide was approved by the FDA in the middle 1980s for the treatment of cardiac arrhythmias. Approval was based on good clinical trials that were positive. In long-term clinical trials, however, it was found that those patients on encainide actually did much poorer than those on placebo. On the Ann Arbor plot, seen in Figure 7, the original would have been in the positive area. Because the long-term study was of such high quality, however, the original accumulated evidence was moved into the negative range. It has just been announced that this drug is going to be removed from the market.

Figure 4. Study design

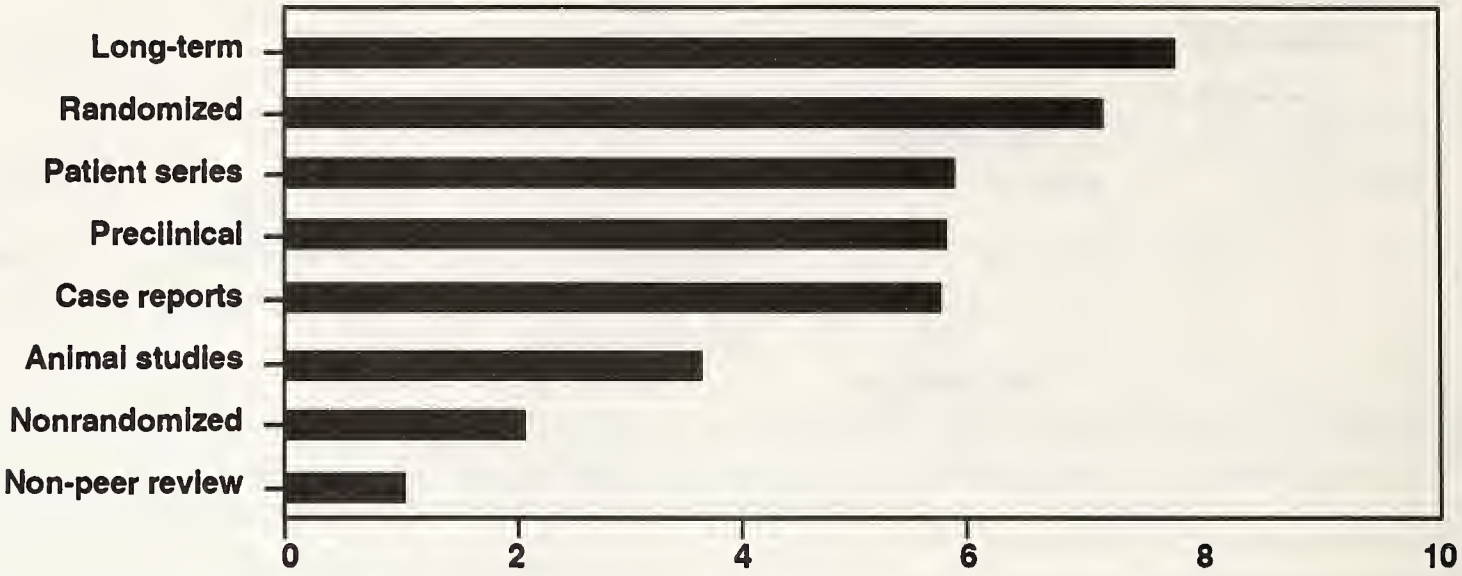


Figure 5. Study design quantification

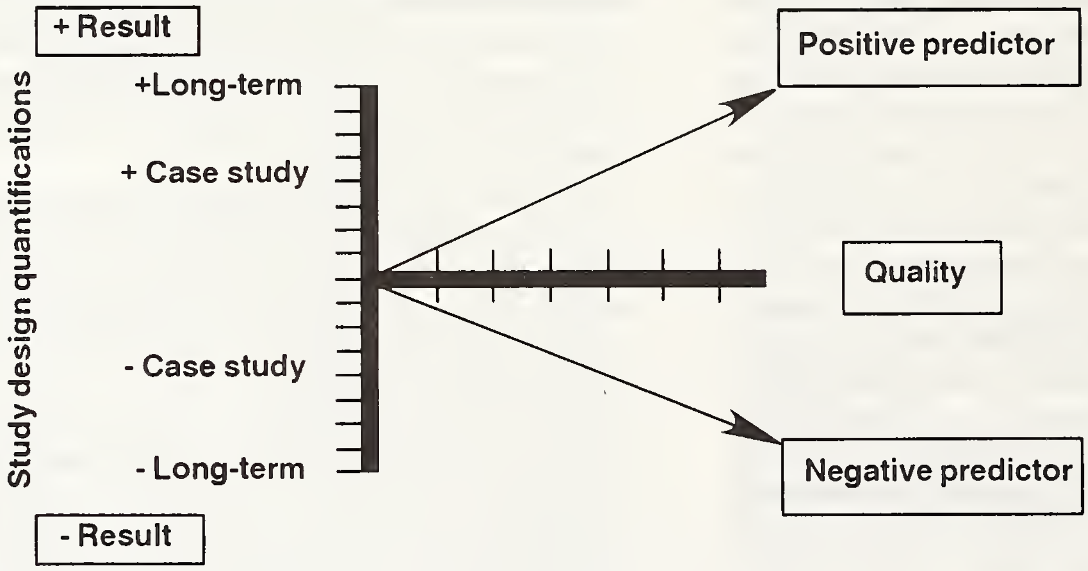


Figure 6. Case example number 1

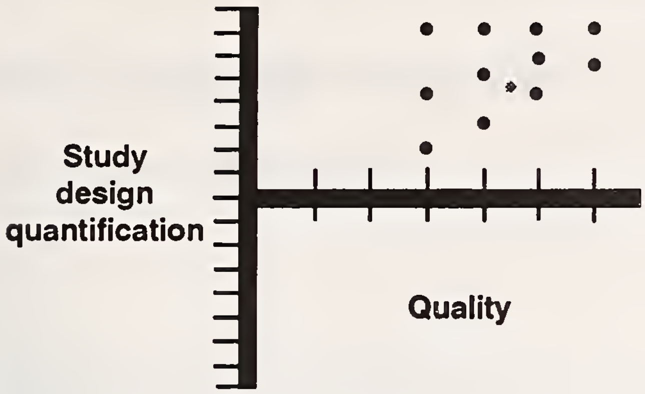
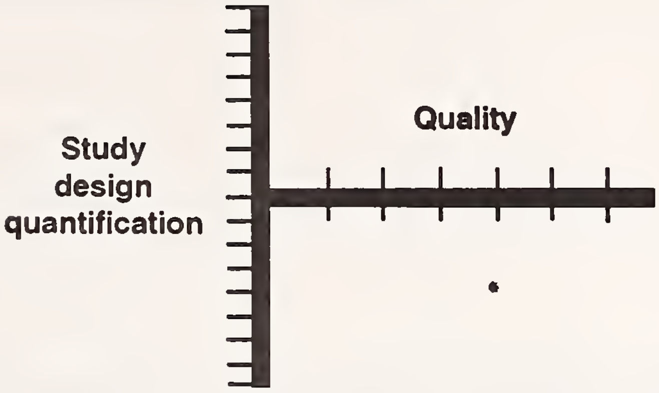


Figure 7. Case example number 2



What can we conclude from this type of discussion? First, we have to conclude that achieving state-of-the-art is a dynamic process and that it comes in gradations as information is obtained. Continual updating is needed. I would like to seriously recommend to the Agency for Health Care Policy and Research that it invest in developing a standard and objective method that can quantify from the literature and assess the safety and efficacy of medical interventions for individual indications. Once this methodology is developed, it should be applied to individual indications, and the information should be published and made available to physicians, patients, payers, and manufacturers so that good patient care and reimbursement decisions can be made. This type of process can clearly demonstrate that there is not a black-and-white distinction between experimental and state-of-the-art, and that instead there are gradations in this process as our knowledge grows, both positively and negatively.

We have been practicing medicine for a long time. We now have the tools to move from the practice of medicine to the science of medicine. We should be using the data that are available to make the best patient care decisions for our patients today and in the future.

Pharmaceutical Perspective

John C. Petricciani, M.D.

The problem of how to distinguish between the use of drugs for investigational purposes and their use in good medical practice has become more acute during the past several years as third-party payers have increasingly declined to reimburse for unlabeled uses of already approved drugs and for medical care costs whenever an experimental drug was used. New procedures in the Food and Drug Administration's (FDA's) approval process in which investigational new drugs (INDs) are made widely available for treatment purposes have complicated the picture even more. My comments will sketch the processes that led to the various categories of drug approval and their uses and suggest mechanisms for identifying drugs for which sufficient data are available to support the realistic expectation of therapeutic benefit.

Approved Drugs

As a starting point, everyone recognizes that FDA approval of new drugs before marketing is the standard and most well-recognized route by which a drug enters into general use in medical practice. However, even though FDA approval has been viewed throughout the world as the "gold standard," in reality universal standards for safety and efficacy were not included in the 1962 legislative changes to the law that governs the FDA, and no such standards exist now. Safety and efficacy are characteristics of drugs that vary according to the class of drug, the patient population, and the stage of disease, to mention only a few of the variables that FDA must take into consideration in reviewing a drug for approval. Congress recognized the complexity of the safety/efficacy issue in 1962 and empowered the FDA to use medical judgment and common sense in deciding—on a case-by-case basis—whether a given drug should be on the market, taking into consideration data from at least one well-controlled clinical trial.

When a commercial sponsor of a drug develops a scientific and medical data base that supports use of the drug for one or more specific prescribing indications, a new drug application (NDA) is submitted to the FDA. When FDA reviews and approves the NDA, it also approves the content of the labeling or package insert for that drug. The labeling identifies those uses of the drug for which the sponsor has conducted studies that demonstrated to FDA's satisfaction substantial evidence of safety and effectiveness.

Off-Label Use and Generally Accepted Medical Practice

In addition to the original sponsor, other groups may undertake research to test a product's potential as a therapeutic agent for medical conditions different from those that appear on the FDA-approved labeling. A specific example is cancer chemotherapy where an agent that has been shown to be effective in one type of cancer may be explored in other types and found to be useful either alone or in combination with other approved drugs. Eventually, such studies are reported in the medical literature, and a greater use of the drug may occur based on such new information. Under those circumstances, the term "off-label use" describes the situation in which an approved drug is being used for indications different from those appearing on the label.

When there is sufficient interest in a specific off-label use of a drug and there are enough data in the medical literature to support one or more off-label uses, there are mechanisms for those uses to be reviewed, for scientific and medical judgments to be made, and for the information to be compiled and made available to the medical profession in an organized manner. The three compendia that serve as reference sources for the off-label uses of drugs are: 1) American Hospital Formulary Service Drug Information (AHFS-DI); 2) American Medical Association Drug Evaluations (AMA-DE); and 3) U.S. Pharmacopeia Drug Information (USP-DI).

It is important to point out several general features that are common to all three. First, they are national in scope in the sense that they represent three independent national efforts to pull together current information on drug use and good medical practice. Each attempts to be comprehensive and current, and we can appreciate how difficult it is to try to meet that objective. Finally, the content of the compendia is based on a review of scien-

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Dr. Petricciani is Vice-President for Medical and Regulatory Affairs, Pharmaceutical Manufacturers Association.

tific data by a number of expert groups. Any one of the three compendia should be considered sufficient for a physician to make a determination on off-label use of a drug.

On the other hand, "accepted medical practice" is dynamic and subject to more rapid changes than can be accommodated by the compendia. The result is that in addition to the compendia, other sources are needed for guidance on what constitutes acceptable off-label use of drugs. In general terms, we would suggest that any off-label use of a marketed drug that has been approved through a formal review procedure with qualified experts should be considered acceptable medical practice. This position recognizes that accepted medical practice regarding an acceptable use of a drug for an unlabeled indication lacks well-defined and strict boundaries; instead, it is continually evolving, as does medical practice itself in the broader sense.

This view is consistent with positions taken both by FDA and Congress. FDA has stated publicly on several occasions over the past decade that the Food, Drug, and Cosmetic Act does not limit the manner in which a physician may use an approved drug and that a physician may prescribe it for other uses or in treatment regimens or patient populations that are not included in approved labeling. FDA pointed out several years ago that the ultimate determination of what is a "standard" treatment as opposed to an "investigational" therapy is not solely the province of the FDA. In short, the FDA review and approval process, including labeling, was never meant to be a mechanism for establishing "accepted medical practice" or to confine a physician strictly to labeled uses for a drug product.

Congress reviewed the issue of what constitutes generally accepted medical practice in determining which drug indications would be covered under the new outpatient prescription drug benefit section of the Medicare Catastrophic Coverage Act of 1988 (PL 100-360). That legislation, although now repealed, required the Secretary, when establishing standards, to incorporate standards from such current authoritative compendia as he or she may select. The conference report stated that the Secretary would be expected to take into consideration one (or more) of the three compendia mentioned previously.

At least on the point of what constitutes "generally accepted medical practice," there is no disagreement among the American Medical Association, FDA, Congress, or the pharmaceutical industry. The compendia can and should serve as important sources of information for both practicing physicians and third-party payers. We strongly endorse the use of the compendia by third-party payers and physicians as prime sources of what can minimally be considered generally accepted medical practice for drug indications. This has obvious significance for the payer in terms of reimbursement decisions, for the physician in terms of knowing in advance what will be covered, and most importantly for patients.

A variation on the role that the compendia might play is to include a general statement in approved labeling that refers to the compendia for additional uses of a drug. This approach recognizes and makes use of an already existing review and approval mechanism for what constitutes generally accepted medical practice and ties the compendia to FDA approved labeling.

When the approved indications for a new drug are unnecessarily limited, this has the effect of contributing substantially to some of the problems we are discussing here. This is especially true for cancer drugs, where at least one-third of medically accepted uses are off-label. The current restrictive attitude toward labeling imposes a very large burden on the regulatory agency, the industry, and ultimately patients themselves because adjustments in labeling must be made virtually on a case-by-case basis.

In summary, the Pharmaceutical Manufacturers Association (PMA) has consistently endorsed the view that full reimbursement should be available for all medical uses of drugs as long as such uses are documented in scientifically respected compendia or the peer-reviewed medical literature.

Supplemental NDAs

In addition to the original indication, a company may continue to pursue research and development of an approved drug for other indications and may eventually submit a supplemental NDA to the FDA with the aim of getting approval for a change in labeling to indicate an additional approved use for the drug. The company's decision to pursue a supplemental NDA depends on many factors. Each company has finite resources in terms of research and regulatory personnel that are needed for the development of new drugs. The finite resource issue also pertains externally—for example, in the number of available clinical investigators. In the overall scheme of a company's research and development strategy, there may not be enough resources to spare from new product development to apply to the preparation of a supplemental NDA.

Another problem is that supplemental applications generally have a lower priority at FDA than new NDAs. There is a tendency for supplementals to drift to the bottom of the priority list even though approval of the new indication may be more important than the original claim. The most likely reason for assigning a low priority to these supplements is the attitude that because the drug is already on the market, availability of the drug should not be an issue. Availability, however, does not necessarily mean that patients will be reimbursed when a physician's use of the drug is different from the labeled indications. There are now about 100 overdue supplemental efficacy NDAs at FDA. If they could be more expeditiously approved, at least some of the present "off-label" uses would immediately become "on-label."

Investigational Drugs

Now we turn to the more difficult and complicated issue of reimbursement for costs associated with investigational drugs. There are at least three different components to consider when we begin to think about reimbursement in the clinical research setting:

1. cost of the drug;
2. costs of any incremental care related to the clinical trial; and
3. underlying costs of the usual and customary patient care.

In 1988, the Institute of Medicine (IOM) issued a report on resources for clinical investigation. In brief, the IOM report recommends that third-party payers should pay for the necessary and appropriate patient care costs that would have been incurred in any case when patients are in clinical studies and that "the marginal, incremental costs above standard patient care costs attributable to the investigational protocol should be borne by the sponsoring institution—pharmaceutical company, NIH, or foundation." In other words, experimental drugs should be considered part of the study costs and supplied free of charge. The PMA Board of Directors reviewed this issue in 1989 and adopted the IOM position as PMA policy.

In general, even before the IOM report or PMA's policy position, the cost of investigational drugs has not been a major issue in terms of reimbursement because pharmaceutical companies, with rare exceptions, have provided investigational drugs without charge. Even when FDA introduced the treatment IND mechanism in 1987, which specifically allowed for cost recovery for drugs that are granted treatment IND status, there was no rush by companies to recover costs.

A treatment IND is, as its name implies, an administrative mechanism that allows broadened access to important experimental drugs for which FDA believes there is sufficient data to show promising evidence of efficacy even though all of the studies may not have been completed or fully evaluated by the FDA. Recent examples of large treatment IND programs are dideoxycytidine and dideoxyinosine which have been used to treat tens of thousands of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients in advance of final FDA approvals. In neither case did the sponsoring pharmaceutical company request permission to recover the cost of the drug.

Where the difficulty really begins is when one tries to sort out patient care costs into those that are directly related to the clinical trial and those that should be considered usual and customary. It becomes especially complicated in the case of cancer and AIDS because many clinical research protocols may, in fact, represent the best, or even the only, available treatment. Therefore, in medical terms and for reimbursement considerations, those treatments should be considered equal to standard therapy, and the associated patient care costs should be covered.

Conclusion

Fundamental to the medically appropriate use of drugs, whether approved or investigational, is a data base that supports the safety and efficacy of the drug in the context of a specific clinical situation.

We believe there are specific thresholds available that should be used for coverage decisions, specifically when:

- a drug has been classified by FDA as approved for marketing or as a treatment IND;
- an additional use of a drug has been specified in one or more of the three national compendia; or
- a new use of a drug has gone through a formal review procedure with qualified experts, such as medical specialty societies and consensus conferences.

In these instances, third-party payers should be willing to cover the costs of those drugs and the associated medical care.

Medical Device Perspective

Candace Littell

The Health Industry Manufacturers Association (HIMA) represents approximately 300 manufacturers of health care technology ranging from "high tech" electromedical and diagnostic equipment to "low tech" supplies and other medical commodities. As manufacturers of health care technology, our members are vitally interested in the decisions that affect the future use and acceptance of our products. For that reason, we commend the Agency for Health Care Policy and Research and the Congress for encouraging this honest exchange of views.

Although many proposals and suggestions have been and will be made during the course of this conference, three overall points should be emphasized. The first is that trying to pinpoint when a technology crosses the threshold from experimental to state-of-the-art status is extraordinarily difficult, even under the best circumstances. Second, universal definitions of where this threshold lies are dangerous and should not substitute for careful, data-driven analysis of individual technologies on a case-by-case basis. Finally, we need to move beyond semantic differences to find imaginative approaches that achieve the needs of patients, payers, and product innovators.

The fundamental question before us is sorting out what is experimental and what is not and finding the line between the two. Even under the best circumstances, determining when a technology crosses the threshold from experimental to state-of-the-art is a difficult and subjective process, due in part to the nature of innovation itself. Unlike in pharmaceuticals, innovation in device technology proceeds incrementally. With a few exceptions, this process—when viewed over time—appears to be a series of microscopic improvements instead of "big bang" creations of universal proportion. At what point along that continuum does a device graduate from experimental to established?

Secondly, some technologies can exist simultaneously as experimental and state-of-the-art. As Elizabeth Brown pointed out in an article in the *New England Journal of Medicine*,[1] oncology provides a good example of this. Although a particular treatment might well be part of a clinical trial and thus fall under the dictionary definition of experimental, in many cases it may well reflect the most appropriate or state-of-the-art care available. Once again, who is to decide into which category these technologies fall?

Complicating the picture further is the role of the user. As we all know, some users are more proficient than others. For example, when used by certain providers, products might achieve a 65 percent success rate; others might reach 75 percent, and still others might exceed 90 percent. In addition, those rates often improve even further as more patients are treated. Studies have found that hospital mortality for certain procedures declined as the number of those procedures performed by the hospitals actually rose.

As users become more and more proficient in using a product, when does that product cross the threshold from experimental to nonexperimental, and at what point does it become state-of-the-art? Is this really a question of grading the effectiveness of users? Is it possible that a perfectly safe medical device can be viewed as state-of-the-art in the hands of one user, yet as experimental in the hands of another?

There is plenty of room for disagreement about where the magic threshold lies between technological adolescence and adulthood. This should send us a clear warning. Trying to pinpoint one threshold that applies to all technologies and arbitrarily forces them to one side of the line or the other is certain to deny patient access to important medical advances—advances that many experts might well interpret as mainstream medical care. These advances may never get a chance to prove themselves—to collect real-life patient data that payers demand—because data do not accumulate until they are used and they cannot be used until they are paid for.

When you stop and think about it, all of this makes perfect sense. How can something as diverse, dynamic, and complex as health care technology have a single time or

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event that determines whether it is experimental or state-of-the-art?

On top of the inherent murkiness in finding this magic threshold between medical experiment and medical mainstream, we must add the issue of costs. As we all know, decisions about what is experimental really are decisions about who will pay for what. Unfortunately, when dollars are on the line, the positions harden, the room for negotiation narrows, and the common ground grows even more difficult to achieve.

This is the picture we are faced with: an innovation process that does not lend itself easily to distinct events or definitions; cost concerns that only amplify the differences of opinion; and a debate riddled by definitional disputes, perhaps more appropriate for a meeting of linguistic scholars than health care professionals.

So, what do we do about it? How do we leap beyond these semantic and fiscal differences? For starters, we have to accept the fact that we cannot remove our mutual biases. We simply have contrasting incentives. Payers will always have the incentive to hold down costs as much as possible, in part by limiting the range of services available. Providers will want to offer patients the best that medicine can offer. Manufacturers will always have an incentive to obtain coverage and payment for their products as quickly as possible. And patients will always want to feel better as quickly and painlessly as possible. Further, we cannot remove the fundamental difficulty of deciding where the threshold between experimental and accepted practice lies. Technological innovation will continue to be a seamless, evolutionary, varied, and diverse process.

Recognizing all of this, we see several key lessons emerging from the picture before us. First, trying to find an arbitrary distinction between what is experimental and state-of-the-art that payers can apply universally across technologies is a recipe for disaster. We simply cannot capture the diversity inherent in medical technology. We are, after all, operating in a gray zone. If we try to create an artificial black-and-white distinction, we will only bottle up young technologies before they have been given a chance to prove themselves.

Second, we have to make medical judgments on a case-by-case basis using solid, well-developed data, not by trying to force dynamic technologies into semantic straitjackets or into "one-size-fits-all" coverage definitions and classifications. Finally, we have to recognize that all sides of the debate have legitimate needs—the payer for data, the patient for treatment, and the product inventors for return on their investment.

When we add up all these facts—that innovation has outpaced its regulatory and payment pigeon holes, if you will; that the line between experimental and state-of-the-art is terribly unclear; that we constantly need more data to make intelligent judgments; and that we find so many definitional differences among parties—it is clear that we must find some kind of a middle ground where the interests of payers, providers, manufacturers, and patients can come together.

Is this possible? Given the divergent viewpoints and definitions, is there really any hope? We think there is. We believe it is time to depart from the definitional differences being discussed and to explore some of the imaginative ideas that might achieve this goal. One idea that has gotten considerable attention and, in fact, has already been discussed during this conference might be termed provisional coverage—a kind of a temporary try out, if you will, for new technologies.

Provisional coverage could begin, for example, when the Food and Drug Administration clears a product for marketing. Alternatively, it could begin on completion of a manufacturer's clinical trials and publication of results. This might occur at various points in the process of development and diffusion of technology. At that point, the product would be covered for a set period of time, perhaps for a few years. This would not constitute final coverage, nor would it go on indefinitely. During the provisional period, the product would be available for use by clinicians in treating their patients, perhaps with some specified limits.

At the same time—and this is the critical part of this concept—additional data beyond those already collected would be generated on the product's effectiveness. This would provide answers to such questions as, "Does it result in appropriate outcomes? Is it well suited for specific indications or particular patient groups? Are there limitations or problems?"

The net result of provisional coverage would be kind of a "dry run" for technology that would address the goals for all parties. It would provide valuable data to private and public payers who need this information to make intelligent and cost-effective decisions—data that emerged from treatment in real-life settings on the front line of health care delivery. This would also address one of the most vocal concerns expressed by payers and one of the strongest criticisms of technology: there are not enough data.

Provisional coverage would provide incentives to innovators who would see a reasonable market opportunity for their work, work that would ultimately rise or fall on its value, not on whether it fits into some arbitrary category. Finally, provisional coverage would provide needed treatments to patients who would no longer have to wait while payers and regulators discussed terminology.

For those who wonder how this might be done, I will point to the recent decision by Blue Cross/Blue Shield to fund the clinical trial of autologous bone marrow transplants. This experiment provides the company with critical data to decide whether and how widely such treatment should be used. At the same time, it allows access to the treatment for many women who would not otherwise get it and have no other alternatives.

Providing this kind of treatment while gathering critical data is reason enough for exploring ideas of this type; there are many others. Another important reason relates to the central question with which we are wrestling at this conference. Provisional coverage would stop us from force-fitting new technologies into arbitrary across-the-board classifications. It would give individual products a chance to prove themselves and force us to judge them on their own merits.

In short, provisional coverage would pave the way for decisions based on facts, data, and actual performance, not on technological typecasting. It would assure us that artificial distinctions would not become barriers to getting the best information possible.

To be sure, final coverage determination would still have to be made, and that would still require some subjective judgment. In all probability, it would lead to a fair amount of disagreement. Even here, however, provisional coverage helps out. The decision would be based on data, not on arbitrary distinctions. The technology would have a chance to prove itself in real-life settings, and all parties would be able to see that the final determination was based more on hard proof than on philosophical nitpicking.

I am not suggesting this is the only imaginative approach that might be tried. Undoubtedly, there are many. Nor is it without shortcomings. It is, however, indicative of the kind of innovative thinking with which we now must proceed. Struggling endlessly over terms that are inherently subjective, trying to apply them to technologies that inherently resist, will only lead to further delays in providing new treatments to patients who need them. It is time to step beyond the semantic differences and propose solutions that judge technologies for what they are and what they do, not how well they fit into this or that corner of Webster's Dictionary.

Reference

1. Letter to the editor. N Engl J Med. 1991;324(18):1291.

Discussion/Questions and Answers - Session 3

Q: [Dr. John Ferguson, National Institutes of Health] Is there any paradigm for provisional coverage for any of the recent technologies that are being tested—provisional coverage by a third-party carrier?

A: [Ms. Littell] I am not aware of any that is specific to the device side of the industry at this point.

Q: [Edward J. Hinman, M.D., Lincoln National Employee Benefits] I am troubled because I think the wrong question is being debated and discussed. There comes a point at which we should move from this phase of experimental/investigational or whatever we are going to call it into the phase of commonly accepted practice. We may even need a new phase, which would be a postmarketing approval period of additional review. Maybe the provisional approach would be a good solution. We have not discussed that point, however, although we are now two-thirds of the way through the conference.

A: [Dr. Petricciani] That is one of the points I was suggesting in the case of drugs and the Food and Drug Administration's (FDA's) development of the treatment investigational new drug (IND) mechanism. What you are suggesting is a black-and-white division between research and what is acceptable for general medical practice when, in fact, as I think most of the speakers have been alluding to, there is this continuum. Nevertheless, within that continuum, you can mark off certain points.

In the case of drugs, FDA makes a judgment that a specific drug has sufficient data to suggest pretty strongly that safety and efficacy are associated with it. To that extent, FDA is willing to let the drug be used for treatment purposes, in the case of dideoxyinosine (ddI) and dideocytidine (ddC), for example, for tens of thousands of patients. In our view, that is the juncture when FDA decides that a treatment IND can move into at least those limited confines of treatment practice.

A: [Dr. Messerschmidt] I think that is one of the points we all made. There is no definition of those terms—of when one ends and the other begins—and when you are dealing with a spectrum, an arbitrary point has to be selected. There may be a different point, however, for each indication and each intervention, and that makes it very difficult. For example, if it is a treatment for a benign disease, we may want a lot of evidence to suggest that safety is an important issue; on the other hand, if it is a life-threatening situation, higher risks may become acceptable, so less defined therapies may become more acceptable at that point.

In the pharmaceutical industry, we are very regulated as to how those data are collected, and they are collected in a very standard fashion. In many other situations in the practice of medicine, data collection is not as rigidly performed, and what we may want to consider is a mechanism for collecting such data, at least a mechanism that will allow us to assess the data in a standard way.

That is not going to happen overnight. Many technologies in standard practice today may have never had a randomized controlled trial. Therefore, if we are going to look for randomized controlled trials to give us all these answers, we are not going to find them. What I would like to see is the development of a mechanism with incentives for doing randomized controlled trials and in which the insurance industry plays an integral part. A partnership must develop between the reimbursers/payers and those with the technology that will allow them to work hand in hand to develop processes that will benefit patients and for which reimbursement will be made. It is only through that type of partnership that we are really going to get out of this bind of trying to define experimental and state-of-the-art.

Q: [Cheryl Austein, Department of Health and Human Services] I share the previous questioner's concern about the specificity of our discussions at this conference, and one question I would like to put to the panel is what are we trying to achieve here? If third parties are to step in now—granted much of what is being practiced today has never been assessed, but the chances of that happening in this decade are low in any event—whose costs are they going to be replacing?

A: [Dr. Messerschmidt] In the pharmaceutical industry in general, we accept a lot of responsibility for the cost of research. That is, in a simplistic way of looking at it, it is our product. We are the ones who are going to make the profit from the product, and therefore we are the ones that foot the bill.

Are there other situations where that is analogous? There is a lot of discussion among other people who tend to have a financial stake in new technologies or new therapies or new applications for which they want someone else to pay, even though they are the ones who are going to benefit. That is one issue.

In other instances, it is purely a public health matter where something needs to be applied or something needs to be understood more thoroughly. Perhaps in those cases it is more of a public sector issue; that is when I think government funding should become more prominent. For example, if a surgical procedure is being introduced and there are questions about whether it truly is an advance, then maybe that should be taken through the public sector.

We have to look at the incentives for the use of the procedure. Are there financial incentives for a group? Are there financial disincentives for another group, or is it something that constitutes a public health issue? In this way, we can identify the responsible party.

Q: [Ms. Austein] Do you mean the problem is that we have not assessed enough procedures and need to bring in additional payers to do that? Is that the problem we are trying to solve here?

A: [Dr. Messerschmidt] Payers are in a funny bind. It was mentioned previously that in many instances, payers have sometimes paid for things for many years which, it later is discovered, have not benefitted patients. On the other hand, there have been times when payers have not paid for things they should have, since these things did benefit patients. The issue that I am addressing—and I am not speaking for anyone else—is to find a way to be able to assess that as cleanly and crisply and early as possible, so that we do not end up paying more than we should and the people who will benefit get the procedures as soon as possible. That is the type of balance that we need to have as a mechanism to assess objectively this information quickly and efficiently.

A: [Ms. Littell] I think what we are really talking about is the emergence of new technology in the health care delivery system. Obviously, our members are very concerned about the funding of those new technologies after having spent considerable resources to bring the product to the point of being able to introduce it into the health care delivery system.

The reason I focus so much on the reimbursement issue is that the definition between experimental and state-of-the-art is most significant and really manifests itself in coverage decisionmaking. That is the critical junction—the meeting point between what is an exercise in trying to establish terminology and what is actually happening in the health care delivery system.

The burden at this point is exclusively on the manufacturer to provide the information necessary for payers and others to make decisions about technology. It is appropriate to look at approaches that might share more of that burden with an emphasis on how to actually get a health care technology that is suitable for appropriate indications into our health care delivery system.

I personally emphasize the reimbursement aspects of this because that is where, in many regards, the critical decision lies as it relates to experimental technology. If you were not, as a payer, making decisions to not cover based on experimental versus state-of-the-art, then I do not even know if we would be having this discussion.

Q: [Robert Pendergrass, National Heritage Insurance Company] I have a philosophical question for all the panelists. Is experimental medicine the state-of-the-art of the practice of good health care, or is it the state-of-the-art of the practice of good research institutions? We need to define the boundaries of good practice rather than the state of research practice.

More specifically, Ms. Littell, presumptive effectiveness is nothing new. I have been in medicine for 50 years, and we have operated on presumptive effectiveness a large part of that time. It has resulted in some significant debacles, not the least of which is the pillage of somebody's treasury, but the more important aspect is the fostering on unsuspecting people of many procedures without efficacy that have no real purpose.

When I make my decisions, I consider the efficacy of medicine and whether it does, in fact, improve the quality of life and the potential for a patient's getting well, rather than whether the medicine is either experimental or investigational.

If you consider the final factor of the proclivity of health care practitioners to never want to get rid of something with which they have become comfortable, you further compound the problem when you adopt a policy of presumptive effectiveness as a basis for payment.

A: [Ms. Littell] As I mentioned earlier, an integral part of any kind of a proposal like the provisional coverage proposal is the generation of information. One of the things that is really lacking now is information about what is appropriate and what is not appropriate and for what patients under what circumstances.

This kind of a proposal is not the answer. There might be many other proposals. We need a process by which additional information about a technology or procedure can become available. That information might not ever get produced under our current system. It is produced in somewhat of an interim process as the technology or the procedure makes its way into the health care delivery system. I could not agree with you more that we need to make better medical decisions, but we need information by which to make those decisions; and this is an alternative that does provide for another source of information.

Q: [Steven Sieverts, Blue Cross/Blue Shield, Washington, DC] There is already in place an enormously expensive process of medical care in this country, much of which represents services that do not stand up very well to cost-effectiveness kinds of scrutiny. When we are experiencing the level of health care spending and the rate of increase in such spending that we are seeing, we quite naturally become conservative about more and more things being added.

The academic centers and the Agency for Health Care Policy and Research could gain a much more friendly response to a more liberal definition by the payers about what is investigational and what is not. They should turn their attention to the proliferation of services used in American communities by hundreds of thousands of ordinary doctors in the face of studies that suggest that many of those services are useless or dangerous; for example, the enormous use of gastrointestinal endoscopy and the continued very high volumes of carotid endarterectomies and coronary bypass surgeries. If there is going to be a partnership, it also must be a compact in which those same entities give some help to this country to do something about the services that are being rendered in such large volumes and that have no substantial apparent benefit to anybody except those who are feeding their families with the proceeds.

A: [Dr. Holohan] I would like to address one of your comments. Our agency has looked in detail at several of the technologies that you mentioned.

Q: [Helen S. Philliou, LDG Reinsurance Underwriters] I would like to know if the providers are willing to talk about the price end of it so that the investigational processes could receive less flak, so to speak, from payers with more timely provision of services and without litigation, without torts and malpractice; that is, clean it up. Many pharmaceutical companies are billing out large amounts for various parts of care that are very expensive. Those costs are passed on.

A: [Dr. Holohan] Medicare has established the payment that it will provide for a liver transplant for a Medicare recipient in a Medicare-certified liver transplant center, and the cost is well below $100,000.

Q: [Ms. Philliou] That's right. What you are doing is passing the burden. You are cost shifting. Medicare keeps it down here, and it comes out of the private payers. That is exactly what is happening.

A: [Dr. Holohan] The representative from Medicare may want to discuss how that figure was arrived at. Medicare believes that is a fair price, and I venture to say—not wanting to speak for Medicare—that you will find many transplant centers wanting to be certified by Medicare to do liver transplants. Do the pharmaceutical manufacturers want to respond?

A: [Dr. Messerschmidt] I can respond for CIBA-GEIGY, not for the whole pharmaceutical industry. We are very concerned about this issue, and we conduct clinical trials before we market a drug to be sure in our own minds—not just the FDA's mind or not just in the physicians' minds, but in our own minds—that the product we distribute is providing benefit to the patient who takes it. The cost of that I cannot address, except to say that our company does not make a proportionately different amount of money from that compared with other areas of the health care industry. As a group, the health care industry is doing better than many other segments within the country.

It is through financial incentives that we are able to take the money that we make and apply it to further research. Of the health care budget today, only 8 percent is pharmaceutical. As I mentioned, the inflation rate this year is 10 percent. So, if all pharmaceutical products were free today, you would still have an inflationary component to health care costs that far outweighed the cost of pharmaceuticals.

In general, many advances in the future will come from the pharmaceutical industry. It is through the technologies that are being developed today by the pharmaceutical industry that many of the chronic diseases that are not amenable to surgical procedures or to many other types of therapies are going to be tackled.

If there were easy answers, we would already have them. These are very difficult diseases without easy solutions. Our company is committed to trying to find those answers. Along with that, we are committed to providing the payers, physicians, and patients with the data that demonstrate efficacy and safety. I want to emphasize the importance of that type of cooperation—of sharing the efficacy and safety data—it should be universal so that the payers can make appropriate decisions about whether something meets the criteria for reimbursement. Hopefully some day, there will be universal criteria for this. If we have the data in our files, but you do not know anything other than what comes out in our marketing tools, that is not good enough. We have to be able to work together so that you understand what you are paying for, and you will see the benefit.

A: [Dr. Ferguson] I would like to respond to some of the people from the third-party payers and to Cheryl Austein. The insurance industry has for many years been paying huge amounts of money for technologies that have not always turned out to be either safe or effective. There are a number of procedures, devices, treatments, and so forth for which Government agencies—for instance, the National Institutes of Health—will not conduct trials or tests because they are not on their research agenda. If no one else is going to test to determine safety and efficacy, I would say that the third-party payers do have a stake in trying to determine what they are paying for, and it seems reasonable to demand some degree of testing before they pay large amounts of money.

Q: [Robert Visscher, American Fertility Society] I would like to ask the panelists a question about possible changes in patent laws that might help in reimbursing some of these studies.

A: [Dr. Rheinstein] The FDA had some experience in implementing the only change that has been made in the patent law to date. It gives patent term restoration for up to 5 years—half the time spent doing clinical trials defined from the date that the first IND becomes effective to the date that the new drug application (NDA) is filed, plus all of the time the company has the NDA in FDA's court minus any time the company was not prosecuting that NDA with due diligence.

Another procedure did not work quite so well. It was to give people exclusivity for newly developed uses. They do get exclusivity—the brand name company is the only company that can put the new use in the package insert—but the pharmacist never knows why the patient is getting the drug, so the generic gets dispensed regardless of the use. Therefore, that one did not work so well.

Clearly financial incentives are very important, and more need to be looked at. I am reminded of FDA's review in 1962 when Congress added the efficacy provisions to the Food, Drug, and Cosmetic Act. We were mandated to go back and look at those drugs that were marketed for the first time between 1938 and 1962 on just the basis of safety without a showing of efficacy. We had to determine whether they were effective or not. For some of the drugs, that was obvious; but for many of the drugs, there was a need for an additional trial, and the companies were told that they had to do the trial by a certain date.

Well, you can guess what happened. If trials were not going well, if it looked as if the trial would result in a finding that the drug would not be better than the placebo, then many of those trials just did not seem to get done. You needed one extension after another. Obviously, some better incentives were needed.

Q: [Roger Winn, American Society of Clinical Oncology] I would like to ask the panel about the parameters for efficacy. I sat on an FDA advisory committee several years ago for oncology where the parameters for efficacy were very rigid. It was either improve survival or quality of life, which could not be measured essentially. There was a lot of discussion then about what was an appropriate measurement of efficacy. Were there surrogate measurements? Ms. Littell, you said not to put things in a straitjacket. On the other hand, the danger is that the issues can become capricious and will vary from board to board. Do you think we should become semi-rigid in our parameters for efficacy, and would you suggest it be by drug or device type? How would you go about the process of bringing some order to this field?

A: [Dr. Petricciani] What we have been seeing over the last several years is a movement to address this specific issue. One example would be the Lasagna Committee that reviewed the agency's procedure for the approval of drugs for cancer and acquired immunodeficiency syndrome (AIDS); the question of the markers for efficacy was one of the central points they addressed. Their recommendation was that alternate indicators of efficacy other than the ultimate one, which is survival in the case of cancer and AIDS and other life-threatening diseases, should be taken into consideration by the agency, including the issue of quality of life.

Those decisions are not easy; in my opinion, the FDA has been moving in that direction over the last several years. A specific example is the recent approval of ddI where they used a laboratory marker of efficacy as the primary basis for approval of the drug. So, there is an attitudinal shift on the part of the agency as well as within the medical community on the importance of using other than those ultimate clinical end points for approval.

A: [Dr. Rheinstein] I think that is correct. The agency is obviously using surrogate end points, as was the case with ddI. The agency is looking at a new form of approval called accelerated approval, the parameters of which need to be fleshed out. The agency is also, however, conscious of things that were approved on the basis of what in essence were surrogate end points in the past that have not worked out. The latest, I think, is encainide, mentioned earlier today, which gives you a better electrocardiogram; but, in fact, more definitive studies show that on average if you take it, you die faster.

With respect to cholesterol- and triglyceride-lowering agents, they were approved on the basis that they lowered cholesterol and triglycerides. I used to have a statement that said whether the drug-induced lowering of cholesterol and/or triglycerides has a beneficial, deleterious, or no effect on the incidence of coronary artery disease is at this point unknown. Some trials were then done. The lipid research clinics trial on cholestyramine showed that, in fact, you can reduce coronary artery disease with cholestyramine.

On the other hand, the World Health Organization trial showed that when clofibrate was used to reduce triglycerides, the incidence of coronary artery disease was a little lower, but on average people died sooner. So, surrogate end points have to be backed up in the long run by the question, "Are you achieving a real effect?"

A: [Ms. Littell] I might also add that generally speaking, the product approval process for devices is becoming more and more rigorous over time. The report I get from our members is that the requirements in terms of submissions are much more rigorous than they have been in the past. In fact, back in May, the FDA issued a memorandum discussing a concept of clinical utility which establishes yet again another level of end points to look at as they relate to a device. Generally speaking, there seems to be a movement for the FDA to become more rigorous in the product approval and clearance process, as it relates to the submissions of our members.

Q: [Keith Harville, Voluntary Hospitals of America] It seems that the period of time from the conclusion of the experimental phase to the marketing approval—which is really the trigger for widespread incorporation of the new technology—is part of this overall problem. What is the FDA doing to streamline the process? It seems from my perspective to be getting longer rather than shorter. There seems to be considerable inconsistency from reviewer to reviewer.

A: [Dr. Rheinstein] On the drug side, the FDA has done a number of things. Over the last 4 or 5 years, we have doubled the number of medical officers, and it is by and large the review by medical officers that has been the rate-limiting step in the process. About six or seven reviews are associated with a new drug application. Separate reviews are done by the pharmacologists, statisticians, microbiologists (if it is a drug with microbiological concerns), chemists, and so forth.

In addition to doubling the number of medical officers, we have introduced a concept called the NDA day, which is a day that the management of the new drug evaluation process sets aside several months in advance to focus on a particular new drug application. Everybody involved in the review has that date in mind as a target date, and all of the various components of the review are ready. Once the discussion has taken place, there is a fixed amount of time between that date and when the agency decision is rendered.

The agency has tried to get more involved with companies in planning the studies that will go into a new drug application so the company can have more certainty that its studies are done in a certain way. If the results turn out as the company has postulated they will, approval will be forthcoming.

All of those things have been done, but even after saying that, there is always going to be a significant lag between the time all the data are in and the time that FDA has an approval out. This includes both the time necessary for the company to write up the studies and the time necessary for FDA to do the reviews.

It is not going to obviate the need for some mechanism to get the product out to people within a time that seems to be reasonable, necessary, and appropriate to their medical care and before FDA has made a final decision.

Q: [Dr. Holohan] I am going to take the prerogative to ask a question, which is about the proposal of provisional approval. That is, what about a payer paying conditionally? How does that address the problem that a hospital or a Veterans Administration Medical Center would have if they know that a very expensive technology is being covered provisionally and they are faced with the choice of buying it or not, not knowing whether it is effective.

Supposing the evidence indicates that it does not work. We have just spent $3 million. Why didn't we wait? A member of a hospital association might call and say, "What should we do? We want to be the first in town. It will cost us $3 million, but it is on provisional status for 2 years and the company will not give us our money back."

A: [Ms. Littell] That is an element of the proposal that would need to be addressed. It may be that you limit coverage during the provisional period to specific sites. Another option is to collaborate in terms of the manufacturer providing the technology and the coverage being offered in terms of the care provided. A number of different options could be looked at within the provisional coverage concept that would bring together the payers and the manufacturers to try to come up with a common solution that would not put providers at such an exceptional risk that they would not even participate in that kind of program.

A: [Dr. Holohan] The concept is fairly straightforward with a surgical procedure, or perhaps the unlabeled use of an approved drug, although that is probably much less of an issue. With devices where a significant capital investment is required, it is a different issue.

Q: [Winifred Hayes, Hayes, Inc., Philadelphia] A question that keeps occurring to me deals with cost shifting, that is, asking insurers and payers to pick

up more of the charges. Normally, when you purchase something, you have a choice as to what you are purchasing. You select the product or the service. Now, I am curious about the panelists' response to a proposition that if payers are being asked to pick up the charges for promising research for clinical trials, what is the response to the payer selecting the focus of that research? Are we prepared to have the insurance industry determine where research should be focused and where dollars should be spent in terms of that research effort?

A: [Dr. Messerschmidt] First, I do not think that CIBA-GEIGY is asking the insurance industry to pay for clinical trials. What we are discussing is, if the trials are done and the efficacy is known, we want to have an understanding that this therapy is now considered to be state-of-the-art and not experimental. That is the definition we are looking at. We are not asking you to pay for our clinical trials.

Q: [Dr. Hayes] I think the situation with drugs is a bit different than it is with medical devices, surgical approaches, and therapies such as autologous bone marrow transplants (ABMTs). Perhaps if we can set aside the drug issue and focus on something like ABMTs with high dose chemotherapy for breast cancer, as an example, it seems to me that carriers and third-party and other payers—self-funded companies—are being asked to share in the costs of promising new technology.

My question is: If we are asking them to share in the cost, do they have a voice in setting the research agenda for the nation? I am not sure that the public at large or payers in particular should set that agenda, yet we are asking them to share part of the burden. I am not sure that I want insurance entities making decisions about what research gets done. In my opinion, the next logical step if you are asking them to pick up a portion of that cost is that they are going to ask for some control. They will want to have some impact on what gets done.

A: [Ms. Littell] In terms of what gets done beyond the information provided for an initial coverage decision, that decision is already being made by payers by exclusion of coverage. For example, if you have a technology that is deemed experimental and not covered, there are several alternatives. You can try to get additional information to obtain coverage; the alternative is that the technology does not diffuse into the system. Therefore, to a certain degree, payers' decisions about coverage—those decisions being based in part on what is experimental and what is state-of-the-art—are leading to a series of events, one of which is going back and producing additional information. So, to a certain degree, decisions about what is covered and what is not covered are having at least an indirect effect in terms of the agenda.

A: [Dr. Messerschmidt] The pharmaceutical industry has two entities that we have to satisfy beyond the physician and the patient—the FDA and the insurer. We have meetings with FDA ahead of time, and we have enough experience that we have clear ideas and interactive discussions about what type of information will be needed to have everyone feel comfortable that the drug is not only safe but also efficacious for patients for the indication being pursued.

That opportunity is not as clear with the insurance industry. Unfortunately, there are hundreds, if not thousands, of insurers, but there is only one FDA. What we are saying is that we all want patients to get treatments from which they will benefit.

If that is your interest, then I recommend that you ask for that information, just as the FDA does. In our situation, we would be more than happy to provide it.

Q: [Roger Strube, M.D., Executive Assets, Ft. Wayne, IN] In regard to the cost of medicine going through the roof, I am not convinced that if we stop doing autologous bone marrow transplants right now, we would really put a significant dent in the cost of medicine or its trends. We have a pervasive failure—not only the American system but also the rest of the industrialized world—in our ability to deliver high quality, cost-effective, and appropriate medical care. It is a failure of the memory base system that we have been using. It is not the cost of ABMTs—it is the millions of complete blood counts and hematological workups that are killing this country. We should be able to save $200 to $300 billion if we could practice effectively. My question really has two parts: one, is there a recognition, among those here or at the NIH, that a failure of the memory base system is causing the lack of quality in the American system in particular? And, two, have you been doing any strategic planning or anything else to get the information to where it is needed?

A: [Dr. Holohan] I am not from the NIH, but I should say that probably the two reasons for the existence of the new Public Health Service agency to which I am assigned are precisely those reasons you have talked about. One is the requirement by Congress that the agency establish a series of clinical practice guidelines; the second is to conduct research on patient outcomes that will look at unexplained variations in medical practice (for example, the rates of hysterectomy in Tennessee versus Vermont which are markedly different for no apparent medical reason) and to provide for the first time large data sets on outcomes as a result of treatment, not using surrogate end points. The test of the outcome is not whether tonsillectomies can safety and effectively be completed, but what happens to the person who has had a tonsillectomy versus another who has not. Is that person any better off? The agency's budget, as was mentioned by Dr. Petersdorf, is only $120 million, which is not a lot of money in terms of the Federal budget nor of Federal health research. AHCPR also conducts health services research, which was cited by both Drs. Petersdorf and Scott, as an activity directly related to the effectiveness and appropriateness of health care.

A: [Dr. Ferguson] NIH does not wish to be perceived as an agency regulating medical care, but we feel that over the years, we have attempted through research to do just what you have suggested. Originally, we did this traditionally, by conducting research and publishing findings. About 1975, Congress decided that was not sufficient and that NIH ought to be involved in doing other things to be sure that those "out in the trenches" are aware of what has come from research. The Office of Medical Applications and Research at the NIH was developed for that reason. We hold consensus conferences about eight times each year to weigh these issues and provide information to practicing physicians through wide mailing and publication in the *Journal of the American Medical Association* and so forth. That effort has been going on since 1978.

This is not sufficient to do the job that I agree needs to be done. The National Library of Medicine has its Medline, as you know, which is a very good way to get information we all use. How many physicians "out in the trenches" are using this source of information? Maybe 10-15 percent, if that. The National Cancer Institute has the PDQ online service for cancer treatments. So, there are a number of things that we try to do to inform the health care community.

I have the feeling that they are not adequate. I do not know if the NIH itself can do more. We are trying. The agency hosting this conference can do a lot more, and NIH works with AHCPR to look at Medicare and CHAMPUS evaluations. So, the problem is real. It is big. I think that the NIH is only a very small portion of the attempt to answer it.

Comment: [Andrea Thomas, Cardiac Pacemakers, St. Paul, MN] I represent a device manufacturer. I think that the time is ripe for payers and manufacturers to have some dialogue on issues of study design for overall effectiveness of the technology. To give you an example of that, we actually have a study going on in the Netherlands which has the input of the Dutch government along with that of our clinical investigators. That particular protocol is a randomized trial looking at the appropriate timing of device therapy as postmedical management. I think there is some open mindedness within our industry to begin looking at these kinds of collaborative studies.

Summary - Day 1

Thomas V. Holohan, M.D.

We have discussed whether we believe that every person in the United States has a right to medical care. Is medical care a right? We discussed patient autonomy, limitations of autonomy, and that those limitations in some instances may be based on available resources.

Questions were raised about whether patients who are seriously ill should be considered in a somewhat different light from patients with less debilitating or intense illnesses. We heard a fairly complete description of the American Bar Association's position on those issues.

With regard to the question of right to care, we were shown data that indicate, as we probably all suspected or knew, that large percentages of our population do not have access to either adequate or basic health care, let alone state-of-the-art care, and that very little emphasis is placed on preventive medical care. As was pointed out, it is likely that the lack of preventive services will increase the long-term cost of health care.

Some interesting themes were proposed which came from several different sources. One of these themes concerned a task force. The National Institutes of Health and the American College of Physicians, as well as one of the pharmaceutical manufacturers, talked about the utility of some kind of systematic structure that could facilitate evaluation of the effectiveness of new technologies, services, or procedures. All of the individuals who proposed this concept talked about the task force being composed of both governmental and private sector individuals.

The pharmaceutical manufacturers stated their belief that the unlabeled use of a drug already approved for marketing by the Food and Drug Administration (FDA) is, by definition, state-of-the-art treatment, although they agreed that the amount of scientific evidence supporting unlabeled uses varies. The treatment investigational new drug (IND) concept was discussed briefly by the FDA representative. Although his was not an official FDA position, it was speculated that a treatment IND may, in fact, represent state-of-the-art use, at least state-of-the-art as classified by medical practitioners in the medical community at the time the designation is made.

In addition to the concept of joint task force evaluations, we heard that more emphasis is needed—particularly in academic medical centers—on the concept of health services research and that such research is likely the best approach for reaching conclusions on effectiveness and outcomes for individual patients.

A proposal was made on how to construct the global review process in almost a quasi-mathematical manner based on the quality and findings of evidence. The point was made that the process of a new service, procedure, or technology going from experimental to accepted, proven, state-of-the-art treatment is in fact a continuum—an analog rather than a digital process. Since even on a case-by-case basis it is extremely difficult to determine precisely when that point has been reached, a proposal was made for coverage to be applied on a provisional basis. This is an interesting concept that we may hear more about.

There was some discussion of liver transplantation. A few points need elaboration. The Medicare process for determining the criteria and the characteristics of individuals for whom Medicare will cover a liver transplant were derived based on published objective data.

It is a different process when Medicare determines how much it will pay initially for a particular procedure. This is basically an actuarial or statistical approach. When this was first proposed to the expert committee assembled by the Health Care Financing Administration (HCFA) to review applications for certifications of liver transplant centers, the office that is charged with determining the actual dollar amount of coverage pointed out that their initial computations were based on reports of 29 Medicare patients, all of the Medicare patients who had received liver transplants in the previous year. Objections were made by some practitioners representing large transplant centers that 29 was not an adequate number on which to do an analysis. The committee was informed that it has been HCFA's experience that with a minimum of 10 cases, reasonably reliable cost data can

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be gathered and that HCFA believed and was willing to demonstrate that those computations based on 29 cases would be unlikely to change if there were 129 cases. The argument was then made that the cost, or the reimbursement level, was clearly a reflection of the fact that most of these people died soon after entering the hospital, thus reducing costs. In fact, none of them died in the hospital.

Whether the criteria Medicare has used in the past—for example, for heart transplantation—are appropriate in each instance is difficult to determine. I would point out, however, that Medicare has made available data which indicate—at least in cardiac transplantation—Medicare-certified centers that perform cardiac transplantations have a significantly improved survival rate, now over 5 years. Therefore, whatever went into each of those specific criteria, the group of criteria as a whole does appear to be related to outcome data, at least up until now.

In the next session, we will hear from representatives of hospitals, those institutions in which much of the care we are concerned with is given. We have representatives of the American Hospital Association and the Voluntary Hospitals of America. We also will hear the Capitol Hill perspective and the payer's perspective.

We could speculate on the significance of what we have been discussing based on some election results. It has not missed the attention of anyone here that a relative unknown in Pennsylvania, whose major platform in the recent election was health care, pulled off what could be described as a rather surprising upset, coming from more than 40 points behind in the polls. Perhaps the public is even more interested than we believed in the issues under discussion here.

Users' Perspective

Henry C. Alder, M.S., M.B.A.

As a representative of the American Hospital Association (AHA), I will address the users' perspective regarding the distinction between experimental and state-of-the-art health care technologies. The AHA represents more than 5,000 hospitals in the United States, primarily acute, short-term, nonprofit hospitals. More than 40,000 hospital managers are personal members, and 5,000 other health care professionals are individual members. We represent a majority of the health care providers in the United States.

Before describing the AHA's perspective, I would like to review why we are participating in this meeting. In April, the AHA received an invitation to discuss the need for guidelines for determining which medical procedures and technologies should be considered experimental or investigational. As the invitation stated, "At present there has evolved little uniformity in the criteria utilized to evaluate the investigational nature of novel technologies. Given the diversity of viewpoints concerning the designation of medical technologies, services or procedures, as investigational versus state-of-the-art medical care, the agency proposes to sponsor a working conference directed toward this question, and a direct exchange of information and expert opinion is a suitable initial step toward the development of a consensus on this issue."

Thus, we are here to share opinions and begin to develop a consensus on medical technology guidelines. This is our opportunity to examine many different points of view, including the perspective of hospitals.

First of all, I want to emphasize that the AHA supports the Senate Appropriations Committee call for the development of guidelines to distinguish experimental and investigational medical technologies from accepted, state-of-the-art medical technologies. We agree that it would be of great benefit to health care providers and practitioners, as well as health care insurers, managed care organizations, and medical researchers, to have guidelines as to which medical procedures and technologies should be considered investigational or experimental and which should be considered state-of-the-art.

Earlier this year, the American Hospital Association made public its proposal for a strategy to reform health care in the United States. This strategy, which was developed as a starting point for debate and discussion, is based on AHA's goal for health care reform in the United States: to ensure that all Americans have access to affordable health care, including preventive services.

The AHA's National Health Reform Strategy aims to achieve value in health care by helping providers and practitioners manage and coordinate care to provide the appropriate care at the appropriate level and cost. To achieve this, the AHA calls for providers and practitioners to be held accountable for the appropriate use of resources, including medical technology.

Providers and practitioners should ensure that appropriate high-quality care is delivered in a cost-effective manner and setting and that care is coordinated across the full range of services and over time. To do so, however, requires the development of medical practice guidelines and the initiation of a more rational approach to the diffusion of medical technology.

We have been told that medical technologies are being introduced every day. This is absolutely correct. An example of the current situation is a Wall Street Journal report that a new, expensive medical technology will be used in every hospital within the next 30 to 45 days, following Food and Drug Administration (FDA) final approval.

The article, entitled "A Dose of Reality: Costly Biotech Drugs Will Pose Hard Choices for U.S. Health Care" (Nov. 5, 1991, pp. A1, A8), describes how Centoxin, a recombinant DNA product, has proved to be useful in treating patients suffering from gram-negative sepsis, a form of septic shock. On FDA approval, the drug is expected to cost $3,000 to $4,000 a dose. Up to 400,000 patients each year are treated for sepsis, but only 1 in 4 can be helped by this drug. If Centoxin were administered to all 400,000 septic shock patients, about $1.5 billion would be spent on these patients. Since it is

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difficult to determine which septic shock patients are suffering from gram-negative sepsis, hospitals would be spending at least $1 billion on patients who could not be helped by Centoxin.

According to Ron Winslow, the author of the article, before it is even on the U.S. market, Centoxin is being decried by some as a budget buster and is reshaping the debate over the costs and benefits of medical technology. In a market crowded with expensive treatments, few have spotlighted so starkly the host of thorny clinical, economic, and ethical issues facing the U.S. health care system.

The article concludes, "All of this portends a turbulent reception for a rich pipeline of other new biotechnology products expected to reach the market in the 1990s. Centoxin is among 21 biotech products awaiting approval at the Food and Drug Administration. Twenty-five more are near the end of clinical trials. Most represent important advances for heart disease, cancer, neurological diseases or other ailments."

Centoxin is a prime reason for the AHA's calling for the development, dissemination, and use of guidelines on new and existing health care technologies and specialized services. Such guidelines would provide practitioners and hospitals with the information they need to make appropriate decisions. Clarifying which procedures are appropriate in given situations and then providing information on provider performance is, the AHA believes, the most effective way to stimulate greater cost effectiveness in the delivery of health care without sacrificing quality or constructing monolithic regulatory structures.

To develop appropriate guidelines and a rational diffusion process, we need to reduce the variability in distinguishing investigational, experimental, and state-of-the-art technologies. From a practical standpoint, experimental and investigational technologies are those modalities, procedures, or services that are still undergoing research or clinical trials, respectively. Information regarding their safety, efficacy, and costs may be limited to a few studies and one or more reports published in established peer review journals. In other words, investigational and experimental technologies are not considered generally accepted medical practice. They are not widely used, nor are they covered for reimbursement.

Conversely, medical technologies that have been adopted by a large number of practitioners are likely to be considered "generally accepted" or "prevailing medical practice" or "state-of-the-art." Because of their widespread use and frequent provider and practitioner requests for reimbursement, they are generally covered.

Although the terms "experimental," "investigational," and "state-of-the-art" are themselves quite clear, it is still difficult to determine at what point a medical technology makes the transition from experimental or investigational to state-of-the-art. Most hospitals recognize an emerging technology as state-of-the-art care when it becomes covered for reimbursement. Proven clinical effectiveness, however, not coverage decisions, should be the primary criterion for distinguishing experimental from state-of-the-art technologies.

In addition to definitional difficulties, hospitals are faced with competing pressures on whether to use or refrain from using new technologies. Patients, for example, want access to high-quality care that is paid for by third parties. Practitioners want to provide their patients with high-quality care and use the latest medical technology, and they want to be paid for their services. They also want to avoid making clinical decisions that might result in future legal action. Payers wish to control payments and ensure they do not pay for inappropriate care. Our current system does not promote a balance of these legitimate yet competing interests.

We recommend bringing rationality to the medical technology diffusion process by incorporating into it an information feedback loop on the appropriate use of medical technology. The individual stakeholders (hospitals, patients, practitioners, payers, etc.) frequently have insufficient information to make wise decisions. To deliver appropriate care, physicians and hospitals need timely information about emerging as well as state-of-the-art medical technology.

To gather enough information for orderly technology diffusion, we propose that a conditional coverage process be established for selected emerging technologies. With this process, technologies that are experimental or investigational would be conditionally covered. Those practitioners and providers who participated in conditional coverage would be obligated to make their results available to receive reimbursement.

Such a process would improve the presently fragmented base of medical technology information and make possible an orderly progression to diffusion. For example, participants would submit clinical data to an independent, private agency charged with collecting and reviewing this information. This agency, made up of hospitals, physicians, businesses, and payers, would report and publish the clinical outcomes obtained by providers using selected technologies. The published data could be used by medical specialty societies to develop guidelines for applying the new technology in the appropriate setting and at the appropriate level. These guidelines could also be used to make interim or final coverage decisions.

A conditional coverage process would not only consolidate information on medical technology, but also make our present system of technology diffusion more rational and help balance the competing interests of patients, practitioners, providers, and payers. The information would help to distinguish experimental and investigational medical technologies from accepted, state-of-the-art medical technologies. It would also help in the development of medical practice guidelines. Conditional coverage could be extended to established medical technologies to determine whether they are still state-of-the-art. Such a process, however, will succeed only if all the stakeholders support it and it is free of regulatory mandates or planned technology diffusion.

Voluntary Hospitals' Perspective

Keith A. Harville

The title of this conference implies that we are dealing with two distinct entities that are not compatible—experimental technologies and state-of-the-art technologies—locked in a struggle to the end with only one to emerge the winner. If that were the case, we could have a great debate on this topic with the most gifted orator emerging victorious.

I do not believe this is a black and white topic. I believe this is a mostly gray topic. My perspective, and I believe that of many hospitals and health care practitioners, is that there is a flow from experimental technologies into state-of-the-art technologies. It is the continuum that ebbs and flows with each scientific breakthrough and each clinical setback.

Perhaps this dilemma could be solved by turning to Mr. Webster. He describes experimental as "the process of testing under controlled conditions in order to discover an unknown effect or law." On the other hand, state-of-the-art is the level of development reached at any particular time, especially as it relates to a device, procedure, process, technique, or science and usually as a result of modern methods. On the surface, there does not appear to be any incompatibility here; once the experiment is successful and can be duplicated in multiple settings, it is the new level of development which makes it state-of-the-art.

So why are we spending 2 days poking at this topic from every aspect? Perhaps the U.S. health care environment was not considered when these definitions were set down. In this environment, when the experimental phase is completed, technology does not automatically become state-of-the-art. There is a chasm which must be traversed for experimental technologies to achieve state-of-the-art status. This chasm is filled with such creatures as Food and Drug Administration (FDA) review, opinion leaders, peer reviewed papers, manufacturers' sales representatives, and reimbursement. For hundreds of medical technology companies, state-of-the-art is a goal so worthy of pursuit that they are willing to spend millions of dollars and many years dealing with these creatures before they reach the other side.

In health care, state-of-the-art is often in the eyes of the beholder (practitioner). It is his or her perspective of state-of-the-art in context with each patient's needs based on the clinical picture, technology available, reimbursement, and liability. Overlay that with the fact that not all clinicians view technology in the same way. There are those who are early adopters, a middle majority, and late or never adopters. The challenge for hospitals is to know when to follow the early adopters while avoiding the closet full of skeletons that can result from blindly following their lead. At the Voluntary Hospitals of America (VHA), we are helping our hospitals find their way through this maze with our technology development program. Although I will be discussing VHA's approach to this question, I know several other not-for-profit alliances are also addressing these issues.

VHA was founded in 1977 by 30 shareholder hospitals. Today, more than 660 service-oriented, not-for-profit hospitals and their more than 190 affiliates are working together to meet the needs of their communities with excellence in patient care and leadership in service. The mission of VHA has remained basically unchanged from its early days to promote the collaboration of selected health care providers committed to common values, community service, and appropriate, accessible, and cost-effective care. VHA seeks to provide competitive advantage to its hospitals through programs that improve quality and efficiency.

VHA provides the management structure for the alliance and makes key services available to its member hospitals, such as:

- Product procurement through supply chain management
- Communications
- Managed care
- Managed information transfer
- Public policy

Mr. Harville is Vice President for Technology Development, Voluntary Hospitals of America.

The technology development program of VHA was put in place to provide early access to leading-edge diagnostic and therapeutic technologies for the VHA member hospitals and their medical staffs so that they can stay at the forefront in providing new medical technologies to their communities. VHA's technology development program consists of a process and the tools to manage that process in four general areas—technology sourcing, technology assessment, agreement development, and agreement implementation.

Technology sourcing can be either proactive or reactive, and I will explore the differences between those two approaches. The real key to success in technology sourcing, however, is our technology development data base. The technology data base consists of 18 interrelational data bases incorporating information on: emerging technologies and the potential medical applications of those technologies, diseases, procedures by type and specialty area, and the companies developing new medical technologies. Maintaining the data base with current, accurate information is a major challenge, and the data base continues to grow and expand on a daily basis. To date, we have over 5,500 records on 70 different technologies and some 500 applications of those technologies, 250 disease or procedure codes and their incidence, and more than 230 companies developing emerging medical technologies. A variety of source documents are used to input information into the data base including: technical journals, government and association reports, company annual reports, company business plans, published analyses of health care markets and technologies, biomedical business conferences, market analysis reports, and national help line resources.

We use two approaches to technology sourcing; one is proactive and the other reactive. In proactive sourcing, we use the technology data base as our primary tool by probing the data base for diseases and/or procedures by incidence, identifying those that have the greatest impact on our hospitals. We then probe the data base for the technologies and applications of those technologies applying to the diseases, procedures, or medical specialties of interest. We seek clinical input to help us identify those technology applications that seem to be on the right track from a clinical perspective. Based on the applications, we use the data base to identify the companies that are developing applications and proceed to an initial company review. The initial company reviews evaluate information gained from annual reports, business plans, and onsite company visits to gain information on products, competitive position, markets and indications being pursued, the regulatory process and clinical trial status, financial status, and references on the company including venture capitalists and clinical investigators. At that point, we decide whether to move forward into the next phase of the process.

The other mode of technology sourcing is reactive. The difference is that here we are being approached by a new technology company that has learned about our technology development program and is exploring the opportunities that may exist through our program, or we are approached by a venture capital company who believes there is a fit between our program and one of the companies in which they are invested. If, based on that initial contact, it appears there could be a fit for that company and its technology, we probe the data base to determine the size of the potential opportunity based on the targeted procedure or disease state and look at what other technologies are being applied to that disease, as well as other companies developing the same or similar technologies. There may also be a window of opportunity to consider depending on the state of development of the company and their FDA status. We then move into the initial company review and decide whether to move forward into the next phase.

The second phase in the process is to perform an in-depth technology and company assessment, basically looking at three general parameters—benefits, technical review, and company review. In the benefits area, we apply the opportunity being considered against our hospital benefits screen which evaluates the potential impact this technology will have on the hospital. We estimate this in four different areas: market size, financial and productivity impact, marketing benefits, and patient outcomes. We are also looking at the benefits to VHA from a sales and revenue potential and where this technology might fit in our technology development program pipeline. At this point, we make a decision on whether to continue to move forward.

The technology is assessed by gaining input from the VHA supply company advisory councils in laboratory, pharmacy, and nursing if it is a technology that would impact one of those groups. We also have committees of physicians in different specialties from VHA hospitals who provide clinical input on new technologies in their specialties. If we do not have the resources internally or through our hospitals to evaluate a new technology, we hire an outside expert to do the technical phase. Again, at the end of the technology assessment, we decide whether to continue to pursue the opportunity. Then we review the company by assessing its business plan, management strength on the business side, management strength in research and development, and financial resources and, if it still seems to be a viable opportunity, decide to move forward.

The third phase in the process is agreement development. At this point, the sourcing and assessment phases have been completed, and we have identified a company with which we would like to develop a technology development agreement. The first step in that process is to probe the company's needs for VHA resources, which allows us to structure a proposal for a working relationship that will be specific to the company's needs. Resources available through VHA that may be attractive to a company developing new medical technologies are: promotion, clinical initiatives, marketing, consultation, distribution, sales, and education. Normally, the company will respond to the proposal by negotiating on several of the points, and the process will end in a signed agreement covering our working relationship.

Agreement signature moves us into the fourth and final phase of our process: agreement implementation. At this point, a product manager is assigned to implement the agreement. The product manager manages the agreement by holding implementation meetings with the key individuals responsible for delivering the resources that have been committed to the new technology company and is responsible for that agreement through product launch and for the term of our agreement.

In summary, it is very important from the voluntary hospitals' perspective to tap into whatever resources are available to follow the progress of experimental technologies being developed that potentially could have an impact on the hospitals' operations in the next 5-10 years. It is also very important for hospitals to be able to identify when those experimental technologies have become state-of-the-art—that is, at what point they must be offering those technologies to deliver the quality and service demanded by their patients and physicians.

The obstacles to hospitals' incorporating new medical technologies, even though clinically the technology is ready to move from experimental into state-of-the-art, are primarily FDA approval and reimbursement approval. The FDA, which has a noble mission of protecting the public from potential harm, must realize that the bureaucratic process put in place to accomplish that also has the potential to harm. When technologies with the potential to improve quality of life, reduce hospitalizations, reduce recovery time and complications, and in some cases, save lives take years to get through the approval process, it begs the question, "Who is protecting the public from the FDA?" Once FDA approval is received, the technology still will not become state-of-the-art until there has been widespread approval for its reimbursement—a haphazard, time-consuming process at best and again, as with the FDA, patients who could benefit from these technologies are the innocent victims.

The Voluntary Hospitals of America has put in place a program, the technology development program, to help our member hospitals gain access to experimental and state-of-the-art technologies by:

- Bringing additional clinical trials to VHA hospitals;
- Providing the hospitals with a competitive technology advantage that attracts patients, physicians, and health care workers;
- Helping VHA hospitals to incorporate new technologies that will reduce length of stay/costs and/or improve productivity/efficiency in their clinical practice;
- Providing early access to those technologies that will improve patient outcomes;
- Providing the educational programs necessary for the successful incorporation of these technologies into clinical practice; and
- Developing new sources of revenue for VHA.

Capitol Hill Perspective

Michael Hash

Members of the Subcommittee on Health and the Environment, Committee on Energy and Commerce, of the House of Representatives are supportive of efforts to commit resources in the public sector that will support more effective evaluation of both new technologies and advancements in clinical care. In particular, they would like to see such activities considered in the larger context of the benefits, risks, and costs associated with advancements in health and clinical care. The idea for creation and authorization of the Agency for Health Care Policy and Research (AHCPR), the sponsor of this conference, originated in large part in our Subcommittee. We are following the work of this agency closely and with a great deal of interest.

My intent is not to present a technical treatise but rather to make a plea that, to the extent possible, decisions about the particular merits of technologies or advancements in health care ought not to be made as part of the political decisionmaking process. Far too often, the Congress, at least in my own view, has been brought in to become the judge for the approval, advancement, or application of a very sophisticated medical care technology. Frequently, it does not make the wisest and most appropriate decisions. As a general rule, the capabilities and training of individuals in or associated with the legislative branch do not qualify them to make these kinds of judgments and decisions.

There is widespread recognition in the Congress of the impact that new technologies and advancements in care have, not only on the delivery of health care services in this country, but also on the resources and budget applied to support public financing programs that provide access to health care services for millions of Americans.

The purpose of my remarks is to present some sense of the Congress' views on some of the issues being addressed during this meeting, issues that deal with how to evaluate and manage the dissemination of new technologies and advancements in care. I want to offer some very general comments about the mood in the Congress concerning the health care delivery system and then discuss what, in my opinion, will be some future Congressional actions that could influence technology assessment; coverage decisionmaking, at least in the public programs; and financing for these new advancements.

There is no question that health care policy concerns—particularly financing of health care services—are demanding more and more attention in the committees of the Congress. To cite an obvious example, there was a political contest in the State of Pennsylvania in which the prevailing candidate made quite a point of advancing the notion that we should establish a national health care program in this country, and that gentleman won the race by a very substantial margin.

Whether that means the voters of Pennsylvania are harbingers of the views of the broader American public remains to be seen, but there is no question that the pace of and priority for health care financing reform have quickened in the Congress. It is fair to say that we are likely to see over the next several years some rather fundamental changes, or health care reform as it is more commonly called. Obviously, Federal resources for financing health care continue to expand. Funds from the public sector now account for over 40 percent of all financing for health care services, so it is not surprising that there is considerable interest in what is happening in this sector of our economy.

It is also fair to say that the impact of advancements in technologies and care is—particularly and singularly—an important factor in influencing the rate of increase in health care expenditures. Therefore, coming to grips with the management, analysis, and evaluation of these advancements is one of the primary objectives of any kind of health care reform legislation that might be under consideration. In addition, the access to health care problem in this country and the cost of health care are inextricably entwined, at least in the view of policymakers, meaning that any sort of progress in this area is likely to involve important changes in how people gain

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access to health care services and how we pay for those services.

Access issues are being debated broadly during this health care reform discussion in Congress, and there is significant disagreement among policymakers. Many believe that we should proceed with health care reform in the direction that builds on our present and long experience with job-based private health insurance supplemented by public financing programs for the elderly, the poor, and those outside of the workforce.

An increasing number of members of Congress believe we should largely scrap this system and install a single-payer public health financing program, either administered directly by the Federal Government or under a series of private contracts. That is the debate we hear about most often—the single-payer versus multiple-payer health reform proposals.

Access and how to provide it, however, are only one side of the coin in this debate; cost control is an equally contentious issue. There is a vigorous debate about how we should manage and allocate our resources for health care services. Once again, there are several schools of thought. First, there is the view that we should put an annual limit on our expenditures for health care services, and proponents believe that over time, the annual limit ought to reach a level that approximates growth in the rest of our economy, since the rate of growth in health care spending is obviously accelerating much faster than the rate of growth in the rest of our economy.

On the other hand, there are those who believe we do not have the right tools—that is, the right information base—on which to make a prospective decision about the level of resources that should be applied to health care in this country. They believe we would be foolish and perhaps inflict considerable harm if we were to proceed down that path. They suggest that we should put into place a rate-setting mechanism that would apply not only in public programs but also to private purchasers of health care benefits. The so-called "all-payer" approach to cost containment does not give us any particular assurance or predictability about where we will end up in aggregate health care expenditures because aggregate expenditures are the product of what we pay for services plus how many services we actually provide.

In addition, some think we might not need either of these approaches, but instead that we need to isolate and remove from the present system the growing administrative costs that have been the target of much criticism in the recent analyses of health care financing in this country. Estimates abound—which may or may not be valid—that from $60 to $100 billion per year are expended for what some believe are unnecessary administrative costs in our present health care financing system. If we could eliminate much of these administrative costs, we would have ample resources to meet the needs of all of our population. We don't have reliable data on how much we could save, and there is no assurance that any future health care financing scheme would not continue to incur substantial administrative costs. I don't mean to imply that there are not a great deal of economies and efficiencies that could be achieved if we had a more rational and well-managed health care delivery system.

In my view, movement on these broad health care reform policy issues will probably turn on whether there can be agreement, at least among policymakers and ultimately on the part of the public, about how to distribute the financing burden of health care delivery in this country and how to control the rate of growth in expenditures. That first issue—how to distribute the financing burden—has been taken up by Henry Aaron[1] at the Brookings Institution in a book that deals with our health care financing and delivery system. He makes the point that, apart from all the health policy issues associated with the health reform debate, there is this significant issue of income redistribution. Most politicians who have given any thought to the risks associated with fundamental reform have identified the potential risks of changing the financing burden on individuals as probably the biggest and most difficult challenge of the health care reform debate.

With regard to a means for distinguishing experimental advancements in health care delivery from state-of-the-art care, this issue has been discussed in the public policy arena for a number of years. There have been many attempts in various guises to address this topic. Ample evidence shows that technology and related advancements in clinical care are responsible for a significant portion of the growth in health care expenditures, generally estimated at about 25 percent of the annual increases in health care costs. In the case of advancements in care that are not within the purview of the Food and Drug Administration (FDA), some have suggested we should have a more rigorous evaluation process for new procedures, techniques, and approaches to the treatment of illness and disease which become available through research and experience in the health care delivery system. Others think we should expand the mandate of the FDA to address more directly the kinds of questions being discussed in this forum. Suggestions have also been made that we set up a national clearinghouse for the evaluation of technology and new procedures, by expanding, for example, the agenda of the AHCPR, or by identifying a new site—outside of Government, but with public and private support—to take up these questions.

Others believe that, as a result of the recent decisions by the Congress to expand significantly resources in the area of medical care evaluation and the development and dissemination of clinical practice guidelines, this process has a larger context and incorporates considerations that are much more appropriately suited to address the issue of when advancements in care ought to move from the experimental stage into general application.

It should be clear to everyone that evaluation and judgments about the appropriateness and effectiveness of technology and procedures should not be a function of the political process. In my view, Congress has been far too willing to step in at the request of various parties and settle questions about the use of technology, at least within the context of the public financing programs, but frequently those decisions carry over and are followed by private purchasers as well. I am appalled at the extent to which statutory, legal language describes a host of very technical and clinical kinds of judgments about coverage and payments that are far beyond the role that law and public policy were designed and intended to play.

My own view is that Congress should basically support and facilitate technology assessment and the evaluation of practice. Actual implementation of this function must inevitably involve a collaborative approach of both the private and public sectors, under the leadership of people with the experience and credentials to make these judgments in a way that will be accepted as credible by the public at large and by practitioners. The end product of such a process should not be limited to determinations of whether new technologies should be made available to the public at large; that is a much too narrow conclusion.

What we need, particularly in the public policy arena, is guidance about a host of other related questions that include how and when to apply these advances, patient selection criteria, center selection criteria, performance standards and costs, benefits, and risk analyses. These analytical tools need to be better organized for use by those who are struggling with how to allocate increasingly scarce resources for health care.

To some extent, this type of broader decisionmaking process has found its way into the Medicare program to define how Medicare approaches a number of advancements (transplants is the most obvious example). An approach similar to this has provided a model for more rational management of advancements in clinical care. As we find health care resources becoming even tighter, the need for this kind of activity will obviously become even greater.

We have had a much more difficult time making decisions about those technologies and procedures that ought to be withdrawn from the marketplace. It has always been easier to make technology available to the public. Much of that technology has been additive, particularly in terms of the cost of health care services. There are tradeoffs that must be made as we introduce advancements in clinical care and practice. What can we safely and appropriately eliminate, or at least eliminate payment for?

In conclusion, we are moving fairly rapidly toward fundamental reform of our health care financing system, which in the end will result in a more explicit limitation on financial resources than we have today. Clearly there will be increasing pressure to politicize the process of deciding what kind of new technology and innovation will be financed, and I hope we can avoid at least some of that politicization.

Most everyone in the public policy decisionmaking process would welcome and urge expanded efforts to create a more credible process to help us move beyond determinations of experimental versus state-of-the-art technology to provide scientifically based advice or protocols on how to manage the diffusion of advancements in health care, given the limited financial resources that are inevitable.

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Capitol Hill Perspective

Michael A. Simmons, M.D.

My perspective on technology introduction is that of a user-clinician on a 1-year sabbatical from the University of Utah to work on the Senate Labor and Human Resources Committee for Senator Hatch. This perspective is not that of Senator Hatch nor of Congress. Indeed, my position on this issue contrasts with that of the individual who was, until very recently, Senator Hatch's senior health policy advisor.

My first personal experience with the experimental versus state-of-the-art debate dealt with a disease in infants—I am a pediatrician and a neonatologist—called hyaline membrane disease, which has been the leading cause of infant mortality, at least in the developed world, for a number of years. In the 1970s, a new drug to replace the missing immune factor in an afflicted infant's lung was developed. An artificial surfactant replacement was first developed in Japan by Fujiwara.[1,2] The efficacy of this replacement therapy was fairly well established by the late 1970s when an approach began toward improved product development using both natural surfactants (that is, surfactants extracted from amniotic fluid from other species and sometimes from humans) and artificial surfactants.

In 1985, a particular product, Infasurf, was reported to be very effective in a well-done study by Kwong.[3] It was effective acutely and subacutely; that is, the incidence of mechanical ventilation was lowered, as were the incidence of oxygen requirement and the duration of hospitalization.

In 1988, about 3 years after the Kwong study, the University of Utah, among 10 or 11 other centers, became part of a phase II controlled prospective study looking at efficacy in a larger population base than was originally reported. At that time I had my first contact with the debate between experimental and state-of-the-art.

From my point of view, this therapy was state-of-the-art, well-established in the medical literature, but that was not the position of the Medicaid financing people. I felt, and continue to feel very strongly, that the drug itself under such circumstances should not be a patient expense in a randomized controlled study, but it came as a great surprise that the Medicaid people, regionally and nationally, denied payment for the entire hospitalization for children who were entered in these prospective clinical trials.

Although some compromise has now been achieved after about 3 years, the cost for children who would otherwise have had longer hospital stays, who would have had a higher mortality—somewhere around 20 percent higher—and who would have had longer exposure to mechanical ventilation and oxygen administration was borne by the hospitals because Medicaid said this was an experimental therapy, not accepted, state-of-the-art care. It was on a protocol, and Medicaid not only does not have to pay for the drug but forces the hospital to pay for the entire hospitalization.

That is an example of what we have been talking about at this conference. When does the therapy move along the continuum from experimental to state-of-the-art? In the example that I have given, one could say, "Well, that's just another example of a bumbling Federal bureaucracy. They really weren't doing it right." Or one could say that this is an example of scientific purity, patient protection, or clearly wanting to find out from a phase II study if something works before insurers—in this case public insurers—are expected to pay the costs.

This behavior is both more threatening and, with apologies, more sinister than either of those explanations. I think that it is simply and purely a cost-control mechanism. It is a glimpse of the future that has profound implications for patient care, for biomedical research and technology, for technology development, and derivatively, for one of the points of light in our economy, which is our biomedical technology industry.

Let me go very rapidly through some health cost information, since one of my themes is that much of what we are going to see, using the code of experimental versus state-of-the-art, is entirely derivative of the cost debate that goes on in this country.

There is no one at this conference who does not know what the Congress is talking about. We currently expend about 13 percent of our gross national product

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(GNP) on health care. Almost inevitably, this figure will rise to about 17 percent around 1996. If the current rate of health care escalation continues, we will expend 38 percent of the GNP by 2030. It is absolutely impossible for that to happen; something will have to give. There is going to be some action, and I want to suggest that there will be no Federal action in any part of the health care debate until there has been some approach to cost containment.

One view is that as long as the American people are convinced that someone else will pay for their health care costs, they are very anxious to have a change in our financing system. Congressman Gradison tells a story of a constituent letter that said, "Dear Mr. Gradison: I am outraged at the savings and loan bail-out proposal. It is an obscenity that the American people are being asked to pay for this. The taxpayer shouldn't pay for this, the government should." As long as in this country we spend someone else's money on our health care, then we are all for revolution, changing the system; but there have been very few examples when someone wants to spend more of his or her own money to fix our health care system.

One of the derivatives of our health cost inflation is that we now spend a decreasing percentage of our budget on research. Federal spending for clinical services and patient care has increased in this country as have Federal expenditures for research.

There was a time in this country, in the 1960s, when we spent about 2 percent of total health expenditures for clinical services and research. In the 1960s, we increased our spending for research at about twice the rate we increased our spending for clinical services. That trend had reversed by the 1980s, when the rate of increase in spending for research was about half of the rate of increase for direct clinical services. This suggests that the more we consume of our health care dollar for clinical services, the less we are willing to invest in the infrastructure that is designed to think more about tomorrow than yesterday.

When we look at how utilization correlates with the increase in costs, we see that it is not the length of hospital stay, the number of admissions per capita, or the number of visits to a provider's office. The classic utilization measures do not account for the increase in costs. They are almost all accounted for by "volume and intensity of service." That is, what we do to a patient per contact is much more expensive—more things that are more expensive are done per patient contact. The target for cost control, perhaps at the expense of many services that all of us have grown to accept from our health care industry, is going to be to limit this increase in the volume and intensity of services.

What are the cost control mechanisms that Congress has suggested? They are rate regulations in the form of so-called expenditure caps or direct rate regulation mechanisms. That is the liberal agenda. The conservative mechanism is the market: make people more responsible for their expenditures, behavior, and consumption.

Everyone is for administrative reform. I am skeptical, however, about the estimates that 30 percent of costs could be saved just by having a better claims processing system.

In the future, medical outcomes research will be designed in a different way, and it is going to be a challenge to every constituency represented at this conference—clinicians, users, patients, providers, hospitals, insurers, and payers. There will be an insistence that we try to constrain the rate of cost increases. We will have to prove the efficacy of new technology, or it will not be paid for. There will be a new requirement for medical outcomes research that goes beyond safety and efficacy in the classic sense—for example, this new drug at $3,000 per dose not only kills a bacterium in a patient, but also saves money. Demonstrating efficacy of a new technology will mean that the combination of the clinical setting and the machine or the technology or the drug leads not only to a better outcome but also a cost-beneficial outcome. There will thus be integration between drug utilization, treatment strategies, and technology utilization to look at patient outcomes.

The issues surrounding definitions of what is state-of-the-art and what is experimental will—and I apologize for my cynicism—blur in the way that we currently think about them and very quickly will be defined by what saves money. It is also likely that we will once again explore a very tension-filled philosophical debate in this country that can be characterized on the one hand by "let the buyer beware," as the final baseline about how we decide what to do, and on the other hand, by a phrase from the *New England Journal of Medicine* editorial, "randomize the first patient."

We have heard at this conference that we have a hard time undoing things that are already established. I am hopeful that there is going to be a big push not to begin using technologies and services without knowing that they work in the terms that I have just outlined.

Dr. Thomas Holohan, during the recapitulation of the first session of this conference, said that there has been a real failure of academic health centers in this area of medical outcomes research. I could not agree more. In fact, of all the sectors that have failed in addressing this problem, the failure of academic health centers to be involved and engage in this area of research is the major one.

We have no infrastructure, or next to none, in the academic setting to begin to address these questions; however, we have to expect more of industry also. Indeed, in this particular debate, I find the hospitals and the payers less at fault than industry and the academic environment for not having the infrastructure present to address this integrated approach to outcomes research.

Finally, I would like to address a comment from Mr. Henry Alder's presentation. As he looked at this continuum between experimental and state-of-the-art, almost by definition, "widely used" meant "acceptable" in terms of state-of-the-art. One of the major problems that we have had in the introduction of technology is that wide use has never, in my opinion, proved correlation with usefulness. Many of the things that we as clinicians do all the time are done because they are professional whim, or because we are afraid of being sued, or because that is how our teacher told us to do it. They have never really been tested. In fact, some of the things that may well be both expensive and not very utilitarian may enjoy very wide acceptance.

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Discussion/Questions and Answers - Session 4

Q: [Robert Pendergrass, M.D., National Heritage Insurance Company] Currently, we are spending 12.2 percent of our gross national product for health care in the United States. This represents 2.2 times more than Japan and significantly more than any other industrialized nation, including our neighbor Canada. Yet by any measure the outcomes of health care in America are no better than and sometimes worse than any of these other nations. Essentially, what is Congress going to do to look at the utilization of the current expenditure for health services to produce a more effective outcome?

I also have a question for Mr. Alder: Both the American Medical Association (AMA) and the American Hospital Association are at present officially espousing universal payment of services as billed by the provider without a substantial overview from any source. In light of the debacle produced in the 93rd Congress with the 93641 legislation, National Health Planning, are you prepared to embrace Federal control of medicine?

A: [Mr. Hash] Was the question, what might Congress do with respect to more economical use of our resources for health care?

Q: [Dr. Pendergrass] That is correct. Currently, we are spending enough to provide universal health insurance for all of our people.

A: [Mr. Hash] The short answer is, on the one hand, that it is not totally clear whether the extra expenditures—and the differences in the health outcomes—in the United States versus those in other countries are explained totally by what we do in our health care delivery system. Some other factors obviously impinge on the health status of the U.S. population; I do not know what the mix of those things might be, but that is at least one argument for why we do not necessarily need to be in line with our neighbors and the rest of the world. We may have a different set of circumstances and problems. On the other hand, most people who thought about the basic question that you are posing have, at least in the interim, been persuaded that they should defer judgment about the use of health care services in view of the effort that we are making in the financing of medical care evaluations and outcomes research and the dissemination of practice guidelines. We think that knowledge is very effective in changing behavior.

A: [Dr. Simmons] As to the question dealing with our expectations, almost all the polling data show what we want and what we will not give up. We want instant access. We will not queue in this country, or we say we won't. We want high touch—which means time, by the way. It is expensive. We want "high tech"; we want it instantaneously available, and, by the way, we want it free. As long as this is our expectation, what the Congress has done mirrors it perfectly.

Eighty percent of health care expenditures in this country go to the non-poor. I always thought that we were supposed to take care of ourselves and that, as a Government, we were supposed to take care of those who are disadvantaged—for whatever reason, structurally, educationally, whatever—those who cannot do it all themselves, hopefully over a very short time period. Instead, we have imposed on ourselves the system that takes 80 percent of Federal expenditures, including almost 50 percent of the expenditures in the Medicaid program, and devotes them to the care of the non-poor.

So when we say what is the Congress going to do, there needs to be some resolution on the part of the populace about what we are willing to pay for. The Wofford campaign in Pennsylvania, which I think was about a lot more than health, talked about a financing system that, from my point of view, is perfectly acceptable; but we tried a similar kind of thing inside the catastrophic program, and it lasted a very short time when people demanded that someone else's money should be used. So I am less demanding of the Congress and cynical about the Congress than I really am about our ethic, at least as it relates to health care.

Q: [Kenneth Nelson, M.D., Office of the Inspector General, U.S. Department of Health and Human Services] I have a question for Dr. Simmons or Mr. Hash. The Food and Drug Administration (FDA) took a long time to review drugs that were less than effective. If you really want services that are less than effective or unnecessary to be removed from the armamentarium, don't you think that it would be appropriate to make that request highly specific, charge an agency with it, and create a timetable?

A: [Mr. Hash] The short answer is yes. We have already given fairly explicit directions about what the timetables ought to be and to some degree the agenda for evaluation of new technology. If you expect people to turn their attention to the equally difficult task of taking things out, you are probably going to have to designate it as a priority and indicate a time period to accomplish it.

Q: [Mr. Nelson] Secondly, if you want to accomplish it, why not try directly with Medicare funding instead of introducing a number of intermediate bodies? It is not clear that the components of the Government can work with each other under the present circumstances.

A: [Mr. Hash] A short, perhaps overly superficial answer is that there is not much interest at the moment for linking coverage in payment directly to findings of clinical guidelines and so forth. There has been at least an unspoken interim willingness to say, let's disseminate information and see what happens to behavior as a result. If we measure practice behavior and find that there does not seem to be any discernible difference in how clinicians practice, despite the fact that additional information is available to them which suggests there should be some changes, then there is a basis for action. Political decisions can be made that say we gave an opportunity for this to take place voluntarily, and now we will take some firmer measures.

A: [Dr. Simmons] What you have just said will happen. I agree completely that it would be better if we were in charge of making those kinds of decisions based on good research findings clearly applied—collective decisions made by all of the entities represented in this room, than if they become highly politicized. In the absence of that, if we and our constituencies try to battle this politically, we will lose. I am not sure if it will be a year from now or two decades from now, but I think what you have said will indeed happen.

Q: [Larry Oday, Vinson & Elkins, Washington, DC] I have a question for Michael Hash. I was intrigued by your comments about Congress's not stepping in on the technical merits of particular technologies, and you indicated that there were already examples in the statute—I assume you mean the Medicare statute—of where Congress has done this. Could give me an example?

A: [Mr. Hash] Yes, I did mean the Medicare statute. You may be right in the end, that it is more of a technical matter of the design of the Medicare program than a statement on the part of Congress about its own judgment on the merits of a particular item. For example, we directed the coverage—in limited circumstances—of a drug to deal with osteoporosis. Again, it has to do in part with the prohibition on self-coverage and self-administered drugs.

The larger issue, however, was that, at least at the time this was debated, some people alleged this particular drug was state-of-the-art and very promising in the treatment of osteoporosis, and that it should be made more widely available. This was viewed as an interim step to accelerate the process, and these provisions were actually put into the statute. However, this is not a particularly desirable way to advance new technologies into the health delivery system.

Q: [Ira Green, M.D., Agency for Health Care Policy and Research (AHCPR). I would like to get back to the question of how one decides whether something is experimental or state-of-the-art. At present, many organizations do this. There are 50 or so organizations listed in the compendium put out by the Institute of Medicine. Several people at this conference have mentioned that the data should be collected and given back to a central source. This was mentioned by Mr. Alder. Mr. Hash said that perhaps a national clearinghouse should be set up for technology, and Dr. Simmons says that one should randomize the first patient.

So my question is, should there be a central clearinghouse? Should it be in the Federal Government? Finally, who is going to spend the money to randomize the first patient, which implies putting a very large number of people in clinical trials where one can really get a very clear answer?

A: [Mr. Alder] I do not think that it must be a governmental effort; it should be a pluralistic effort, first of all. We have said several times that this would be an opportunity to show the positive side of our efforts and our combined experience and look towards some type of collaboration in this effort. I do not have a particular model in mind per se, but in terms of financing, perhaps there should be some global financing, and all parties should participate. One of the next steps to accomplish this might be to reconvene this type of session or create a task force to examine how this initiative could be managed.

A: [Dr. Simmons] I represent an academic institution, a pretty good one, and one that does a lot of research. This topic is something about which we have an absolute vacuum. In general, the structures that we depend on in this country for addressing research questions—and these are research questions—are really in very short supply. Most of us look to this agency [AHCPR] for many of these things, and we all know what the obstructions to this agency are. So Government has to have a big role, not so much as referee, but as funding agent for research.

I still believe in investigator-initiated research. It is the best way to get at research questions, but there will probably be a need for more directed research—that is, the request-for-proposal (RFP) kind of research. If this does not happen voluntarily, it will have to be made a requirement—and it will be an expensive one—that those producing new technologies will have to help in the funding of studies to prove utility. So the funding sources, as I see them, would be the National Institutes of Health (NIH) and AHCPR for increased funding to do investigator-initiated research and more RFPs. Some type of requirement is also needed, even if it is regulatory, about what gets paid for (a Medicare kind of model of what gets paid for) as well as major incentives or punishments for those who develop new approaches to help fund the research that establishes utility.

Q: [John Cova, Ph.D., Health Insurance Association of America] I have a question for Mr. Alder. I agree with what you said about a rational diffusion of technologies. However, institutional providers have two antagonistic forces in operation here. With what you are proposing and with the marketing techniques and procedures that institutional providers are using, how can you reconcile your idea of a rational diffusion with the current aggressive marketing practices in some institutions? For example, with autologous bone marrow transplant, how would you achieve a rational diffusion?

A: [Mr. Alder] We must be realistic, those types of practices do occur in some hospitals in the United States, and hospital practices regarding marketing vary from one institution to another. Obviously, some are much more aggressive and others are not aggressive at all. We have a continuum, if you will, of approaches hospitals use in how they offer services—not only in how, but in what services. I may be wrong, but I don't think the more aggressive ones are the majority—the typical community hospital is directed toward providing services to its community and understands the needs of its community for different types of care.

We all know that to start up autologous bone marrow transplant services is extremely expensive. It is still considered to be "investigational" for a number of disease entities. In the past, hospitals had to be aggressive in order to establish new capabilities because of the lead time needed and because there are some territorial issues in communities where there are two or more hospitals serving a fixed population. I am not condoning that as the best way to go, and I do not think the Association is condoning that either. We would like to find opportunities where two or more hospitals in a community could collaborate in offering services. I understand that some legislation is being discussed on the Hill regarding seed money or grant money for hospitals in a community to look at avenues of collaboration; this of course is barring Federal Trade Commission controls or concerns. This issue will have to be resolved in the very short term.

Q: [Max Boller, M.D., MedCenters Health Plan, Minneapolis] Of the reviews that have come from AHCPR, I recall the one on surgery for carotid artery stenosis, which I thought was very well put together. Should this agency be doing things faster and getting them out to us sooner so that we understand that the practices at the University of Pittsburgh or the University of Minnesota for transplants are phase I investigational, phase II investigational, or standards? Or, should this be done by a private agency financed individually? If it were directed by the agency—and there is a mandate for doing that, Dr. Holohan—what would be the cost of becoming current so that you could answer the questions within 3-6 months of being asked?

A: [Dr. Holohan] First, the document that you refer to on carotid endarterectomy was an assessment, and the assessments are not aimed at practice guidelines. They are a medical and scientific review of data on one specific technology. What would it cost to get them out in 3-6 months? Right now the time involved in producing one assessment is 12-14 months. Part of that time is irreducible because of the process involved with *Federal Register* notices that tell the world what we are doing and solicit information from any who care to supply it and subsequently, our review of submitted information. A staff of five produces about 10 assessments and about 5 shorter technology reviews per year. With such a small staff, we are close to our irreducible minimum turnaround time.

It costs about $1 million a year to run our office. We have gotten out the shorter reviews, particularly to CHAMPUS, within 1 or 2 months. So it can be done in that time period. There have been many debates about various novel approaches to increase the size and productivity of the technology assessment office, but perhaps that could be left for another time.

Q: [Dr. Boller] In other words, if I write my Congressman and say that the Government can help me get answers in clinical practice, then I need $1 million and five more people for 15 reports a year; is that right?

A: [Dr. Holohan] Yes, except you mentioned answers on clinical practice, and you must distinguish between functions of the agency that include, but are not limited to, technology assessments. There were discussions by members of the panel about the production of clinical practice guidelines, which probably relate more toward what you are saying about appropriate clinical practice than a specific technology assessment. There was discussion on outcomes research and a discussion of health services research, which is slightly different. Dr. Simmons mentioned that. Interestingly enough, Dr. Petersdorf from the Association of American Medical Colleges mentioned insufficient health services research as a failing of academic centers. So with respect to producing a technology assessment, yes, I agree with your speculation as to what resources it would take to do them faster and do more of them, but those do not define clinical practice, except in a very micro way.

Q: [Dr. Boller] Dr. Simmons stated that we know the obstructions, but I do not. Is the obstruction politics, money, or clinical practitioners' lethargy?

A: [Dr. Simmons] All of the above. If you wanted to take a vote for more centralized authority or dollars for this agency, among the people at this conference who represent various constituencies, you would get a lot of negative answers. I am new to this issue, and I had the same incredulity that you are expressing about why we can't just get on with it. There are many people who have different views about whether this is the right way to go about deciding the difference between my view, professional whim, and proven validity of therapy. Many of us here in this room are part of the obstruction.

A: [Dr. Ferguson, National Institutes of Health] I would like to agree with a number of things that were said by Dr. Simmons; that the fault is not in the Congress but in ourselves that things are going awry regarding these issues of technology assessment and experimental versus state-of-the-art. I would like to offer a challenge to Dr. Simmons and other participants who will go back to the academic health centers. Going along with what Dr. Petersdorf said, the medical education system in this country by and large ignores many of these issues in educating medical students. The challenge is to try to introduce these issues in the medical schools' curriculum so that we have knowledgeable clinicians and physicians, dentists, and nurses who can take up some of these issues in their life's work.

I was at one time in charge of a medical school curriculum for teaching about the nervous system at Case Western Reserve, and I know how hard it is to get things into the medical school curriculum. But, I believe that is a challenge which applies especially in neonatal care and teaching and intensive care units. It is hard to disregard "high tech" involvement in all our residency programs in every field. Many of these aspects are emphasized, and the aspect of health services research is minimized.

Q: [David Metz, Medical Data Source, Bethesda, MD] One approach to health care financing in some other countries involves regional allocation of dollars. I wonder if there is any consideration on the part of the Congress or the Administration to look at allocating Federal funds on a regional basis and allowing folks within those regions to make allocation decisions as to how many positron emission tomography units or trauma units or transplant centers or whatever ought to be available. The whole question concerns application of technology, both state-of-the-art as recognized or accepted, as well as new technologies and of using the Government as a way of letting those decisions be made on a regional basis whether the starting point be the current AHCPR or whatever.

A: [Mr. Hash] I think there is some consideration of this matter, particularly regionalization of resources, especially if—and maybe it is not a question of if but when—we deal with the matter of setting a limit of some kind on the growth in health care expenditures. Many proposals have already been introduced into the Congress that discuss allowing limits to be established at a regional level and decentralizing the allocation decision to States or regions or whatever. We tried to do a little of this in the 1974 National Health Planning and Resources Development Act, something I think someone described as a disastrous 93641. A component of that was a regulatory scheme for, in some instances, the approval of not only technology, but also procedures, services, and capital investment. There is no question that, for the most part, it was not linked in any particular way to the consequences of financing these things, but it certainly proved that the American people, at least the people involved in comprehensive health planning, had an insatiable appetite for whatever was proposed to them because virtually nothing was ever turned down. It gives one pause about people's willingness to make these kind of tough choices. The flaw in that particular experience was that it was not linked in any direct way with the consequences for financing care.

A: [Dr. Simmons] We have a very hospitable history for thinking that the utility model, the West German model, or whatever you want to call it, for expenditure caps on a regional basis will work well in this country. I lived through the certificate-of-need process from a user's point of view, and I learned a lot about how trickle up happens much faster than trickle down in this country. Every person in this room, including people on the panel, make much of their living because they are very good at gaming a system—we are experts in America at gaming a system. From what I have read about the West German utility model system, they tend to behave better about agreements and compliance and so on than we do in this country. So concerning the idea that we will be able to have expenditure caps, my fear is that we will freeze an equity in place; it will happen because of an assumption that we know what we have now is good, and we are going to keep it good but slow the rate of growth in health care costs.

I do not see one single example of a heavy rate regulation mechanism in the health care industry in this country that has accomplished its goal, even though philosophically I do not have any objections to rate regulatory methods. The data do not show that such systems have worked well here.

Comment: [Earl Steinberg, M.D., Johns Hopkins University] It has been said consistently during this conference that what we are lacking are data, and the data are of two types: primary data that give us some idea of the value of a technology or its safety, and secondary data analysis where we evaluate and synthesize the available data. The thought that the former type of data is going to be generated in 3-6 months is simply unrealistic. It is possible, however, with adequate staff to synthesize and evaluate data in that sort of a time period. I heartily disagree with the notion that what is lacking is the infrastructure. That is not to say that I think we would not be better off if we had more infrastructure, but that is simply misplacing the problem. People in universities with the capability to do these forms of assessments are numerous. The methods, as we heard from Dr. Messerschmidt, for synthesizing these data also exist, as do the criteria that enable us to distinguish between experimental and state-of-the-art technologies. What is lacking is the money to support the assessments, and secondly, the resolve or the incentive that results in systematic data collection. The notion that one can get that without giving up something is probably wrong, but unless we impose or develop a system by which all new technologies are systematically evaluated, we will never know the answer to any of these questions.

My second point is that even when such a system is in place, we unfortunately are still going to have to make hard, tough decisions because most new innovations provide some benefit but at high cost. Eventually, someone still has to bite the bullet and make a decision. I have no problem with that type of decisionmaking on a decentralized basis.

Comment: [Dennis Cotter, Medical Technology and Practice Patterns Institute, Washington, DC] I am amazed; these discussions, for the most part, took place with the creation of the National Center for Health Care Technologies some 13 years ago. A process had been put in place to do much of what we are talking about. Maybe the time was not right then, but it probably is now.

Comment: Gregory Morris, M.D., Blue Cross/Blue Shield of the National Capital Area] I feel strongly that the solution to these problems will require a collaborative and cooperative effort from the kinds of groups and organizations represented here. I do not think that it needs to be assigned to the Government or to the academic medical centers. In order to get a balanced solution, we all must participate.

Second, there is a perception that there are deep pockets, whether they be Government or insurance companies, which will pay for all the things that we desire. We must realize that deep pockets are no deeper than each of our own pockets and pocketbooks here because the dollars that the insurance companies pay for these services are, in fact, dollars that your employers put in, dollars that you have contributed and/or dollars that do not go into your pocket. And the same applies for those dollars that the Government spends.

Payer's Perspective

Anne Marie Hummel

As a representative of the Health Care Financing Administration (HCFA), I will discuss from the Medicare perspective the process for covering experimental versus state-of-the-art technologies and the procedures and criteria that the Medicare program uses in making coverage decisions on what technologies it will or will not pay for.

The Medicare program was established in 1965 under Title XVIII of the Social Security Act, and within the context of that law, it provides for a broad array of services and benefits under Part A and Part B of the program. Part A deals primarily with inpatient hospital, skilled nursing facility, and home health services. Part B deals with outpatient and physician services. The Medicare program specifically excludes some services from coverage, but what it does not do is provide an all-inclusive list of what items and services should be covered.

Congress vested in the Secretary of the Department of Health and Human Services the authority to make specific coverage decisions under what we have commonly referred to as the "reasonable and necessary" determination clause in the law. That provision of the law basically provides that "...Notwithstanding any other provisions of this Title, no payment may be made under Part A or Part B for any expenses incurred for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." The term "reasonable and necessary" has never been fully defined in regulations, but in practice, longstanding Medicare policy has interpreted it to mean safe and effective, not experimental or investigational, and generally accepted in the medical community. For purposes of the Medicare program, we use the terms "experimental" and "investigational" synonymously.

The Medicare program could not possibly make a national coverage decision for every item or service that we could cover under the program, so therefore most of our coverage decisions are made by our Medicare contractors who pay individual claims. For fiscal year 1991, we expect that Medicare will have paid close to 600 million claims for services for approximately 34 million beneficiaries at a cost of over $120 billion. Only about 10-20 issues of national significance, however, are addressed to HCFA's central office each year for a national coverage decision. Contractors are, in fact, a frequent source of referrals to the central office for national coverage decisions. If we make a national decision, then it is binding on the contractors, and they have no discretion within the bounds of that policy to change it.

In January 1989, we published in the *Federal Register* a proposed regulation that outlined the criteria and procedures HCFA uses in making national coverage decisions for new health care technologies. We have been pursuing diligently publication of a final rule, which we expect will be published next year in the *Federal Register*.

Before I describe the process by which we make national decisions, it is important to set forth the criteria we consider in making "reasonable and necessary" determinations because they obviously play a big part in what eventually is paid for under the program. For the purposes of this conference, we also should distinguish what is experimental versus what is considered state-of-the-art. State-of-the-art, in relation to Medicare coverage, could best be described as those services for which we have made a positive determination about safety and efficacy because those are the key criteria we consider in making decisions.

If the service is generally accepted by the medical community in the setting and for the conditions for which it is used, or if its use is based on authoritative evidence, then Medicare makes a finding that it is safe and effective. In exercising the discretion used in reviewing individual claims, contractors look toward "generally accepted in the medical community" to mean reliance on published medical literature, such as scientific data or research studies that are published in peer reviewed journal articles, or on a consensus of expert medical

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opinion and consultations with their medical staff, local medical societies, and other health experts as necessary.

Authoritative evidence in the context of the Medicare program has generally meant evidence based on clinical trials and randomized clinical trials. In the final coverage rule, we will attempt to describe in more detail the context of those terms because in the proposed rule, we speak to them only in broad terms.

There may be evidence that supports a conclusion that a service has been shown to be safe and effective in some settings but not for all settings or conditions, and in those cases, Medicare may not cover the service. Coverage may be provided with certain limitations, however; for example, our policy covers heart transplants and more recently liver transplants subject to specific patient and facility selection criteria.

Some of the other papers given at this conference have mentioned data sharing and data collection. Under the heart transplant program, we have asked for data to help us make a determination whether coverage should be changed after the period of years since we initially established coverage.

Drugs and biologicals that have received full Food and Drug Administration (FDA) approval for marketing are considered safe and effective under the Medicare program when they are used for the indications for which they are approved in their labeling. For unlabeled uses of FDA-approved drugs, our contractors have the discretion to make payment based on reasonable and necessary determinations in each individual case.

In developing the final coverage rule, we received many comments on the applicability of the authoritative compendia in making these decisions for unlabeled indications, and we intend to address that issue as well in the final rule.

Devices that are approved by FDA under the premarketing approval (PMA) process are considered safe and effective by Medicare. Contractors use their discretion in approving for Medicare coverage devices that are cleared for marketing under the 510-K process. This is primarily because FDA does not make a "safe and effective" determination in clearing such devices, as it does in approving a PMA, but rather in clearing the device for marketing under this authority, FDA determines that the device is substantially similar to devices that were on the market before the advent of the 1976 Amendments to the Food, Drug, and Cosmetic Act. Therefore, these "substantially similar" devices do not always garner Medicare coverage.

Experimental or investigational considerations generally mean that a service is being furnished for research purposes, and that means that there are still questions of safety and efficacy that have not been answered. We have had much discussion at this conference about clinical trials and about having a collaborative effort in funding clinical trials. It should be pointed out that a medically necessary hospital admission and health care services coincident with the administration of an investigational protocol may be payable under the Medicare program.

In an outpatient setting, any medically necessary services, including complications that may result from an investigational treatment, would be covered. When the sole purpose for a hospital admission is to receive an experimental therapy, however, it would be a noncovered service and would not be considered a medically necessary hospital stay. Therefore, in such a case, no payment would be made.

Drugs or biologicals that have not completed FDA's full market approval process are considered experimental or investigational. We have determined that treatment investigational new drugs (INDs) fall into that process. We did make an exception, however, to cover group C cancer drugs a number of years ago based on strict oversight and protocols established by the National Cancer Institute (NCI) and assurances of significant evidence that effectiveness was shown in the treatment of one or more tumor types. Devices in an investigational device exemption status or devices that have not been approved by FDA are also considered by the Medicare program to be experimental or investigational, as are services that are not widely used.

Appropriateness is another criterion for determining what is reasonable and necessary. That simply means that the setting and the specific services furnished are commensurate with the patient's condition and that the services are performed by qualified practitioners who have met training and education requirements.

We have proposed to add cost effectiveness as a fourth criterion. We predict that if we were to use this criterion, only a few decisions would be subject to formal cost-effectiveness analysis. Under our proposal, cost effectiveness would be an appropriate consideration only when used to compare a technology with already covered alternatives.

Some of the factors that we might consider if we were to use cost effectiveness as a coverage criterion would be if significant medical benefits are provided by a new technology notwithstanding its cost; whether the technology is less costly and at least as effective as an alternative covered technology; or whether the technology is less effective and less costly than an existing alternative, but a viable alternative for some patients. Under the cost-effectiveness criterion, we will not deny coverage of a technology simply because of its cost. That the

Medicare program cannot deny coverage based on aggregate costs is important for us to keep in mind.

If we were to use cost effectiveness as a coverage criterion, we would publish in the *Federal Register* methodologies that we would use in making decisions based on this criterion. We publish our proposed approaches so that the public is aware of our intentions and is given an opportunity to be involved in the process.

As indicated previously, most of our coverage decisions are made by the individual Medicare contractors. There has been a lot of concern because that obviously leads to some variation in coverage policy. This is particularly true in the oncology community, as shown by the difficulties that many cite in receiving payment for unlabeled indications of approved drugs. This is not to say, however, that regional variation is necessarily a bad thing. As pointed out earlier, it would be impossible for us to try and nationalize every coverage decision. There are general rules for determining when an item or service would be covered under Medicare. These rules include primarily whether the item or service is within the scope of benefits provided by the statute, whether there are any statutory bars or limitations affecting coverage, and whether there are any specific exclusions.

The participants in this conference have alluded to prevention and preventive services. We have not talked enough about that. It should be pointed out that in the Medicare program, preventive services are generally excluded under the statute. Only recently has Congress legislated limited coverage of such preventive services as screening mammography and screening Pap smears. We could possibly see more of this in the future; however, for Medicare to be paying generally for preventive services would take a statutory change.

When an issue comes to us for national consideration, a number of factors influence whether we undertake to develop a national coverage decision. For instance, we might look at such a decision if the service:

- Is likely to be used in more than one region in the country;
- Has the potential for rapid diffusion and application;
- Is a significant advance in medical science;
- Is a new product for which no similar technology is already covered under Medicare; or
- Might be a significant expense to the program.

More often, national coverage issues are considered because there is substantial disagreement among the experts regarding the safety, efficacy, and appropriateness of the service or because there are inconsistent coverage decisions by our contractors.

We have established a technology assessment process by which we develop national coverage decisions, and part of the first step again comes from our contractors. The Coverage-Payment Technical Advisory Group (TAG) comprises medical directors of our contractors. This group represents a cross-section of all of the carriers who pay Medicare claims. The TAG initially discusses issues that might require a national coverage decision and whether the issue should be sent to the HCFA physicians' panel for consideration of a full assessment.

If we decide that an item or service requires a national coverage decision, the HCFA central office does a literature search, often using the National Library of Medicine to locate all of the medical literature and data that are available on a given item or service. We prepare a background paper and present it to the HCFA physicians' panel.

This panel primarily comprises Public Health Service (PHS) Commissioned Corps officers who work for HCFA or the Public Health Service (PHS). The panel meets about every 6-8 weeks, depending on the agenda items. We ask them to look at the issue and make a recommendation on whether we should refer an item to the PHS for a technology assessment.

If we proceed with that process, then the Agency for Health Care Policy and Research (AHCPR), through the Office of Health Technology Assessment, will publish a notice in the *Federal Register* announcing the area to be assessed and affording an opportunity for other Government agencies, medical specialty groups, experts, or anyone who has an interest in the issue to receive information in order to make appropriate recommendations to HCFA. That information is then synthesized, and an assessment and recommendation are prepared and forwarded to the HCFA. The recommendations represent a consensus of the PHS, FDA, and NCI.

Based on PHS recommendations, HCFA will issue a national coverage decision. Most often, this is done through our manual instruction process; however, if a recommendation is to withdraw coverage of a previously covered item for which we have a national coverage decision, we publish a notice in the *Federal Register* and ask for public comment before we finalize the policy.

Most of our national coverage decisions involve procedures or devices. We do not normally refer drug or biological issues to the PHS.

The PHS may suggest that an item be reevaluated or reconsidered at a later time. Also, we may reevaluate our policies when significant new evidence or information that was not available at the time an assessment was conducted becomes available—we might then determine that the issue should be reevaluated based on this new information. Normally, that means there are newly available published scientific data which show the effectiveness of the item or service.

Virtually no technology is absolutely without risk or totally effective in all cases; the greater the risk, the greater the need for proven effectiveness. The HCFA has an obligation to provide access to high-quality health care for its beneficiaries and its recipients, and this means that we have an obligation to cover important new technologies, but we also have a fiscal responsibility.

We need to consider the solvency of the trust funds and fiscal constraints. We would not want to use all of our available resources for a technology that only marginally improves health or for which questions about its safety or effectiveness have not been answered.

A number of suggestions have been made at this conference as to how we could come to a meeting of the minds. Medical outcomes research and established practice guidelines obviously are important considerations.

We have heard discussions about establishing a task force to develop guidelines on experimental versus state-of-the-art technologies. A suggestion was made for a provisional coverage process for life-threatening or serious illnesses where we could pay for a technology while allowing for collection of data.

One of the words heard often at this conference is "research." It was suggested that we all should "chip in" and pay for clinical research at an early stage; by doing so, we might be able to determine effectiveness more quickly and save money in the long term. One of the problems from the perspective of the HCFA is that, as was intended by Congress when it established the Medicare law, we are not a research agency. Answers will not be found by payers alone nor by researchers alone. Everybody needs to think about this, and we need to think about changing our own behavior in terms of what we want, what we are willing to do to get it, and what we are willing to give up to get it.

The Medicare program has undergone change over the last 25 years. The Catastrophic Coverage Act was the most significant change in the law since its inception; more recently, we had physician payment reform. In my opinion, any proposed changes in which Medicare would consider covering investigational therapies would have to be reconciled with the need to maintain the level of currently provided benefits.

It has been suggested that trying to deal with the issues politically is not the most appropriate way to go. We know, however, that over the years much of what we have has obviously come from Congressional action.

We have heard many interesting ideas advanced at this conference. There are no simple answers or any one answer, but it certainly seems that this is the start of what obviously will be an ongoing effort.

Payer's Perspective

John L. Cova, Ph.,D.

The Health Insurance Association of America (HIAA) is a trade organization that represents 300 private health insurers who provide coverage to approximately 95 million Americans. Since this conference has been using the "R" word quite liberally, we would like to provide you with some information as to HIAA's position on reimbursement.

As a trade organization, we do not recommend that a technology be reimbursed, nor do we recommend that reimbursement be denied. Our function is to provide our member companies with what we believe to be a comprehensive review of objective scientific data. It is then left to the discretion of our individual member companies to use that information in whatever way they see fit.

The HIAA is actively involved in technology assessment. We use a forum approach. Thus far, we have completed two assessments and have planned a third. The first assessment concerned the clinical application of positron emission tomography to cardiac imaging. The proceedings from that forum are available from HIAA as a public document. The proceedings from the second assessment on the application of positron emission tomography to brain imaging will also be available from HIAA. Our third medical technology assessment will address the role of pancreas transplantation in Type I diabetes.

As the number of new technologies continues to increase and the capacity to pay for them diminishes, payers face allocation decisions that sometimes place them in opposition to the traditional goal of the physician to do everything possible. The patient advocacy role of the physician is not inherently wrong and should not be abandoned.

Reconciling the apparent conflict between payers and providers, however, is becoming increasingly difficult. This is due in large part to the absence of a universally acceptable definition that payers can use when formulating coverage policy for experimental strategies whose advantages over traditional or state-of-the-art technologies are questionable. Thus, formulating rational coverage policy for many new technologies frequently poses difficult allocation decisions for private and public payers. The HIAA's role in developing definitions of experimental and state-of-the-art will consist of providing a payer's perspective of what is required of the definitions rather than the definitions themselves.

As a representative of HIAA, my role includes providing an overview of the policy issues that we believe need to be addressed in order to develop a technology assessment protocol that can be used to determine whether a new technology is experimental or state-of-the-art. From a payer's perspective, the designation "state-of-the-art" should correctly identify technologies that are judged clinically effective according to reports in peer reviewed scientific literature and/or preponderant expert medical opinion. "Experimental" should clearly indicate that there are insufficient objective scientific data to determine if a technology is clinically effective. It should be emphasized, however, that the mere proof of clinical effectiveness may not always signal a change from experimental to state-of-the-art.

The new technology must offer significant advantages relative to competing conventional clinical alternatives or doing nothing. Thus, a change from experimental to state-of-the-art should also signify that there are sufficient objective scientific data to show that the new technology offers significant clinical benefits and advantages relative to other technologies used for the same purposes.

The diffusion of a new technology that is just as good as one already in place simply adds a layer of redundancy that further contributes to escalating health care costs. "Just as good" is not good enough; it must be better.

In the process of formulating definitions of experimental and state-of-the-art, it is crucial to specify the sources of scientific data, the criteria, and the assessment methods that will be used to determine if a technology is ready to move from experimental to state-of-the-art. In the case of emerging technologies, data from highly reliable sources, such as the peer re-

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view literature or randomized clinical trials, are not always available. If data sources other than those contained in the peer-reviewed literature can be considered credible, then these sources and the circumstances under which they are used in making a determination should be described.

For example, when preliminary data strongly suggest that a new technology offers significant advantages, it may be necessary to rely on other sources of information such as expert medical opinion. If data and evaluations from institutions other than academic or recognized research institutes are used in making a determination as to whether a technology is experimental or state-of-the-art, the composition and sources of financial support of these organizations need to be ascertained.

If and when universally acceptable definitions of experimental and state-of-the-art come into existence, an appropriate technology assessment mechanism will need to be correctly applied. From a payer's perspective, an appropriate technology assessment protocol will correctly determine whether an experimental technology has evolved into a state-of-the-art technology.

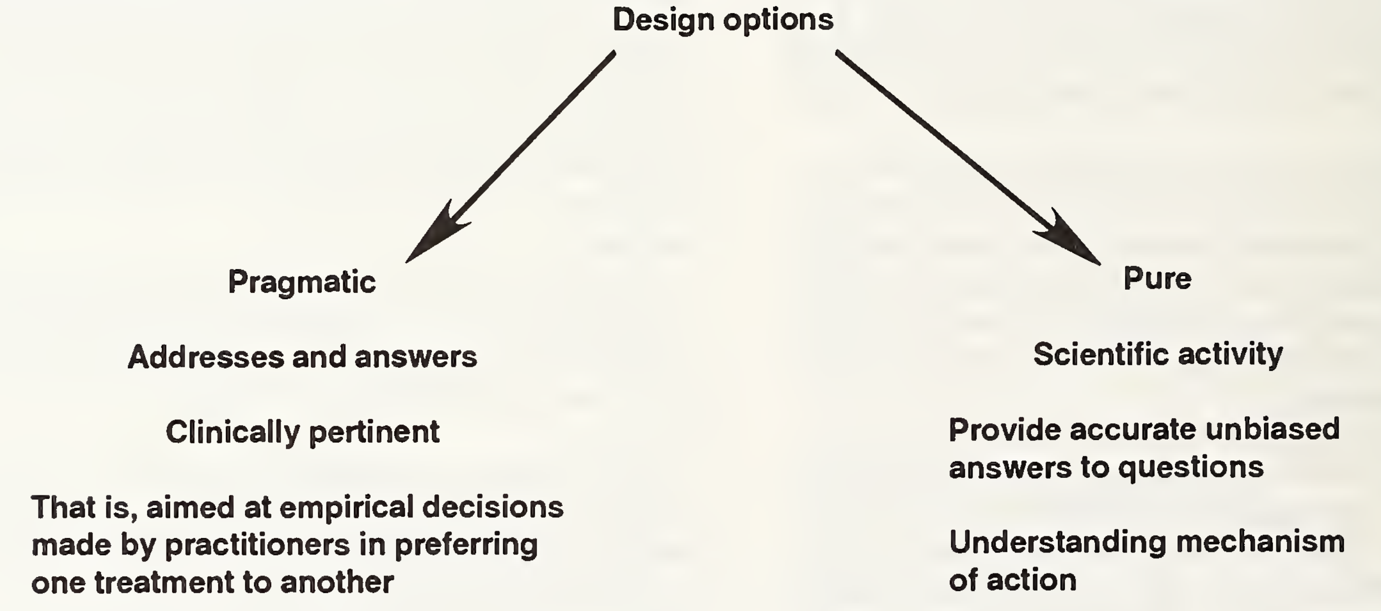
The design of an appropriate assessment protocol must address specific policy issues that will ultimately determine the scope of the assessment mechanism (Figure 1). For example, the strategic policy must clearly define and state the question the assessment is asking. If the experimental technology is a diagnostic test or procedure, should the assessment confine itself to answering questions about efficacy and parameters of test performance—such as sensitivity or specificity—or should its scope be broadened to include issues that compare its clinical effectiveness relative to conventional technologies used for the same purpose? Should proponents be expected to provide clear evidence of improved patient outcomes? Should the scope be broad enough to consider issues of cost effectiveness, such as marginal utility?

Obviously, a payer would prefer that a change in status from experimental to state-of-the-art be based on information from assessments with the broadest possible scope. Such assessments, however, are not always possible or even practical. Thus, strategic policy must not only define optimal assessment criteria but must provide a rational alternative that defines a baseline or minimum requirement for assessments when practical or ethical considerations preclude more comprehensive evaluations.

Strategic policies that determine the design of assessments that focus on experimental technologies must also consider the purpose of the design. Should assessments of so-called experimental technologies be initiated only if there is good reason to believe that it will provide incontrovertible evidence about effectiveness?

Since assessments may not always provide a clear-cut answer that satisfies all interested parties, the strategic policy should define a comfort level that must be achieved when assessment outcomes show that the experimental technology is only slightly better than the established technology or only better under specific circumstances. In other words, if the experimental technology is as good or better than the conventional tech-

Figure 1. Design options

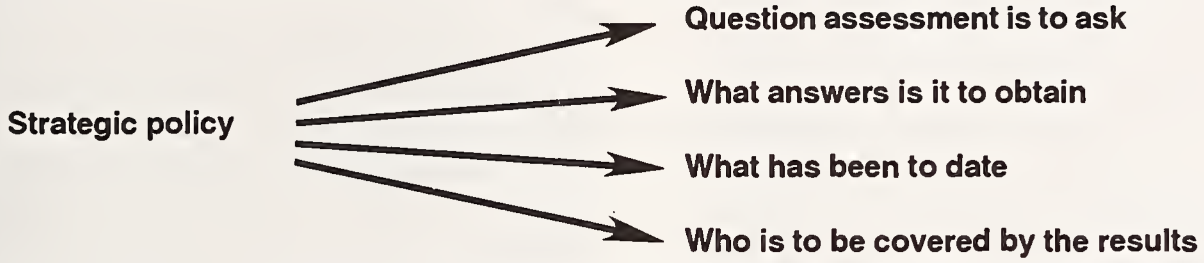

Design options
Pragmatic
Addresses and answers
Clinically pertinent
That is, aimed at empirical decisions made by practitioners in preferring one treatment to another
Pure
Scientific activity
Provide accurate unbiased answers to questions
Understanding mechanism of action

nology 10 percent of the time, can that be regarded as sufficient evidence that it is no longer experimental or must the new technology be better all of the time or somewhere in between?

If technology assessment results are used as a primary determinant in coverage decisions, the policies governing the assessment methodology must be structured to ensure that the evidence on which the assessment is based includes all that has been done to date. This approach ensures comprehensiveness of the assessment. In certain instances, a thorough and careful evaluation of what has been done to date may preclude the need for an immediate assessment.

The last crucial element of the technology assessment policy must consider who is to be covered by the results. That is to say, the policies that define the objectives of the assessment must weigh the needs and consider the end user's perspective. For example, an assessment that focuses exclusively on safety and efficacy may be adequate for a manufacturer or a regulatory agency but fail to fully address the needs of a payer who requires information about clinical effectiveness or the effect of the technology on patient outcomes. A payer prefers technology assessments based on design options that address clinically pertinent questions (Figure 2).

Figure 2. Design of technology assessment


Strategic policy
Question assessment is to ask
What answers is it to obtain
What has been to date
Who is to be covered by the results

There are two basic design options that can be followed in doing a technology assessment. One can follow what is referred to as a pure approach and design the assessment so that it provides evidence about the mechanism of actions of a technology. Such a pure approach is a scientific activity and provides accurate and unbiased answers to questions. Payers, on the other hand, would prefer what is referred to as a pragmatic design. Such an approach addresses and answers questions that are clinically pertinent—that is, questions that are aimed at the empirical decisions made by practitioners preferring one treatment to another.

Both of these approaches are valid; however, in my opinion a pragmatic approach would be much more beneficial to a third-party payer.

Payers' Perspective

Susan Gleeson

The topic of this conference appears to have expanded. We were to have addressed experimental or investigational treatments, but much of the discussion has been about reimbursement. Therefore, my paper will try to cover both topics.

First, let me address the investigational exclusion. What is the history of it? Where did it come from? Why do insurers have it in their contracts? Second, what kind of a process do we have at Blue Cross/Blue Shield to determine whether a technology is investigational? Third, who is going to pay for medical research? We have a serious problem here, and we need to address it. Finally, I will review some of the activities of insurers on these issues.

First, where did the experimental exclusion come from? Some people think it is recent—that it is something that has been put into contracts. When we checked, we traced it back to the 1950s and payment contracts with hospitals and with subscribers which specified what would or would not be covered. Although the exclusion language was generally defined as something not having regulatory approval, the intent was to rule out things that were still being tested.

What has changed over the years is not the nature of the exclusion but the monitoring and scrutiny of it. There was a time in America when our biggest concern was access, not cost. We routinely paid for many things so access would not be jeopardized. When costs became a major concern and our accounts demanded that we as insurers do something, one consequence was a closer monitoring of contract exclusions.

When insurers put in specific programs, they began to identify many instances of payment for inappropriate care. Insurers paid for inappropriate care because there was no close monitoring. They paid for hospitalizations that were not necessary. They also paid for investigational procedures. Since the advent of closer monitoring, however, these situations are being identified and in some cases denied, causing the current concern about what is investigational and what is necessary.

How do we make these decisions at Blue Cross/Blue Shield? We have been conducting evaluations at the Association and advising our Blue Cross/Blue Shield Plan members for about 20 years. We work with a medical committee and assess whether a particular procedure or device should be recommended for coverage or whether it is investigational. Our process has evolved over that time and has paralleled developments in the science of technology assessment. As the science has been updated, so has the process we use.

In 1985, we examined our process, conducted a year-long study, and concluded that steps should be taken to ensure that our assessments are objective—that if anybody else looked at the same information, they would reach the same conclusion. We believed that the criteria we used should be public so that when any device manufacturer, provider, or subscriber asked about our position, we would be able to document it. That is, we could say, we go through these steps and this is our conclusion.

We worked for a year with Dr. David Eddy. He has a national and international reputation in technology assessment, and he helped us to define the critical issues. What are we looking for in a technology assessment, and what results do we want?

Our first criterion is that the technology must have final approval from a regulatory body. This is part of the contract, but it is also important for performing an efficient technology assessment. Without regulatory approval, it makes no sense to go forward. This is a critical but not necessarily a sufficient condition.

So, the technology must have final approval from a regulatory body—in most cases, this is the Food and Drug Administration (FDA); for drugs, final approval means being automatically covered. Devices must also meet FDA approval, but this does not necessarily mean coverage. Most of you probably know that many of the devices that are approved by the FDA are approved through a process that does not consider safety and effectiveness. Rather, they receive grandfather approval because they are similar to a device that existed prior to 1976 when the device amendment was established.

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Regulatory approval is a threshold criterion. Anything that does not meet our subsequent criteria would be considered investigational. Therefore, it is quite simple: without the appropriate approval, the technology is considered investigational.

There also must be scientific evidence that permits conclusions concerning the effect of the technology on health outcomes—that is, there must be some published evidence about the benefits and risks of using the intervention. This allows us to do an assessment. If there are no published articles, it would be considered investigational. If there is nothing that can be concluded from published articles or the studies are flawed—such as not having a control group—the technology would be considered investigational.

Most importantly, the technology must improve the net health outcome. When we examined our process and various issues including language used such as "safe and effective," questions arose. For example, exactly how safe and how effective is it? Is it highly effective? Or is it only marginally effective?

We decided to use concrete terms that we could identify and quantify in the studies. Our use of net outcome includes several components. Does the technology's use lengthen or improve the quality of life? Does it increase the ability to function?

The important point is that we are addressing the bottom line of health care. Frequently, you may have an intervention that makes a difference within the person. It lowers blood pressure; it increases blood pressure; it shrinks a tumor; it does something. The result is a physiological change, but you want to know whether that change make a difference in the bottom line. Does that person live longer? Is the quality of life better, or is the ability to function better?

If this criterion, which we think is the most critical, is met, then we go on to ask if the technology is as beneficial as technologies currently existing. We do not want to approve coverage for technologies that are less effective than what exists.

The final criterion addresses whether net improvement is attainable outside the research setting. We might stipulate that the technology should only be used in certain settings, but this will not stop the technology from being approved.

So if we go through the whole process and find that all five criteria are met, we say that the technology is eligible for coverage. If none of the criteria are met, it is considered investigational.

An important issue addressed at this conference is what the term "investigational" means. In Blue Cross/Blue Shield Plan contracts, it only means one thing; it means that all of the criteria are not met. We do not argue about whether it is in a clinical trial; a technology could be in a clinical trial and still be paid for. For example, frequently in cancer research two standard treatments are compared. Just because they are in a clinical trial does not make them investigational. The only critical thing for Blue Cross/Blue Shield is whether the treatments meet the criteria.

How do we conduct this process? The staff that performs our technology assessments are Ph.D.- or M.D.-prepared. They all have a strong background in the review of research literature. They go through the criteria in writing their assessment—whether there was approval from the FDA; the number of relevant studies in the published literature; the types of studies, whether they were randomized and controlled or case series; what the outcomes were; what the benefits and risks were—and finally reach a conclusion. Then the draft assessment goes to a review body within the Blue Cross/Blue Shield system. It is called the Medical Advisory Panel and is composed of physicians who review the draft and decide whether it is accurate and should be disseminated to Blue Cross/Blue Shield plans. This year we began adding external members to the panel. We now have on the panel a noted oncologist from Dana Farber, a technology assessment expert, and the head of the assessment program at Johns Hopkins. Next year we intend to expand it further.

Also, for life-threatening situations, we want to be sure that we have all the data so we do not wait for publications. For a life-threatening issue, we invite the researchers to present their data to the panel. For example, we recently did this for lung transplants and autologous bone marrow transplants for breast cancer.

Finally, our goal is to open our process to the public, and we are moving in that direction. Our Blue Shield of California plan conducts all of its technology assessments in a public forum, and the Association will be doing that, too, so that everybody can see the evidence.

One of the interesting things—and it is being echoed throughout this conference—is that people think insurers do not pay for certain things because they cost too much. I just reviewed our assessment process, and cost is not a criterion. We do not address cost; we do not even include how much something costs. Our assessment is strictly clinical, and the clinical decision is made by physicians.

Also, there are two nonvoting members of the panel who assist us in keeping the discussions true to the criteria. We do not accept any anecdotal evidence from proponents. David Eddy sits on the committee as a nonvoting member and monitors criteria use. We also have a nonvoting ethicist, Al Jonsen, from the University of Washington. He has been with us for several years and helps us with ethical issues. For example, is it medically necessary to be pregnant? This question is relevant to in vitro fertilization. Or is it ethical to limit access by age? For instance, should organ transplants only be for people under age 55?

Many of today's concerns would be lessened if insurers did not use the term "investigational." It would be much clearer if we just said this is what we pay for and this is what we do not pay for. Everybody has a different definition for investigational, so reaching a consensus on how the term should be used, particularly if reimbursement is involved, is not likely.

When I began, I said that the issue of paying for medical research is fundamental to this conference. Why is it an important issue today, and why is Congress interested? Why is there a push for insurers to pay for technologies that are investigational? Why is this happening now and not 5 years ago?

It is partly because much of the previous funding has dried up. Another presenter at this conference said that more money is going into health care delivery than into medical research. The Federal commitment to medical research has slowed. There is less relative money. The philanthropic foundations' contributions to medical research have tightened; we just do not have the funding that we need for medical research.

What can we do about this? Some say the Federal Government should do more. That is not practical or realistic. The political will for increasing the budget for medical research does not currently exist.

Others say, make the insurers pay, but we are just a pass through. You could require us to pay for everything that is investigational, and that is an option. Only it is counterproductive. Right now, we have 37 million Americans who are uninsured, 50 percent of whom are employed but cannot afford insurance. So making us pay for investigational procedures will only add to our premiums and result in more people being uninsured. You cannot increase the cost without decreasing access in today's environment.

This issue is important. It is an issue for which we need a public debate, but everybody involved in health care must contribute. One group cannot solve this.

A demonstration project in which Blue Cross/Blue Shield is involved epitomizes the current struggle. The issue is the use of high-dose chemotherapy with autologous bone marrow transplants for women with breast cancer.

One out of nine women in our country gets breast cancer. Current treatments are not very effective, particularly for the later stages where survival is no better than 20 percent. Recently in the oncology community, researchers have started using autologous bone marrow rescue in conjunction with very high dose levels of chemotherapy, which sounds logical. They believe that increasing the dose levels will be more effective, so they remove the bone marrow, give very high doses of chemotherapy, and then reinfuse the bone marrow.

Researchers started using this treatment in women in desperate situations, and it reached the point where many of the researchers concluded that this was the only chance some women had—autologous bone marrow transplants as part of their breast cancer treatment. The data, however, did not show any improvement—that these women were better off than if they had received conventional chemotherapy. That is unfortunate, but then you might ask, why are we paying for this treatment if it is no better than what currently exists. Its effectiveness is questionable, since women live as long with conventional chemotherapy.

In the summer of 1990, there were an unprecedented number of law suits over this treatment and whether it is investigational. The key issue was who should pay for it. It is very expensive. Most people cannot afford it themselves, so we were sued when we denied it. We believed we had solid grounds, but it was very poor public relations. People thought that the only alternative they had was being cut off.

We could have paid. That would have been easy. It would have been simple, resulting in no more law suits and improved public relations; however, if it was not as good as conventional chemotherapy, we would be stimulating wide diffusion, and some day down the road, we would conclude that it did not work. This story is similar to that of radical mastectomy.

Or we could help collect needed data. The only consensus that existed was that a randomized trial was needed, so why not put together a randomized trial and see which is better? We contacted the National Cancer Institute (NCI) and decided to work with them and fund the trial.

It might be a prototype for addressing similar issues. The NCI decided what the protocols would be. There are two for stage II and two for stage IV. The NCI decided which institutions would be involved. We negotiated the fee with the institutions. We said that the procedure is investigational, and that is what we still say. We do not consider it eligible for coverage. Completely new contracts were written. We said that we were supporting a clinical trial involving an investigational procedure to determine if it works, and if it does, we will routinely cover it. If it does not work, we will put our money somewhere else.

This is a good example because it shows how perceptions change. There were researchers—and I am not criticizing them—who said that women needed the procedure or they would die; but once the clinical trial was agreed to, the researchers were no longer saying that the procedure was better than conventional treatment. Indeed, assigning people at random to treatments in a clinical trial is unethical if one treatment is clearly superior.

Now the researchers are saying that the treatments are equivalent. We really do not know which one is best. As insurers, our perceptions changed, too. We originally said that we would not pay, but now we are paying about 50 percent with the institutions covering the rest. It is a partnership. The patients have no financial responsibility. We think this is good. Maybe it is a prototype—I don't know—but it has served us well here. Instead of everybody arguing over whether it is investigational, we said that we would find a way to help share the cost. The researchers went forward with a very important clinical trial, and I am not so sure that it would have been conducted had we not decided to pay. So there are some lessons to be learned.

There are other issues that we still need to address. How are we going to get data? We have the criteria, and the principles that I reviewed are accepted both nationally and internationally. Everyone agrees that you need a regulatory body; you have to know something about the benefits and risks; you should improve health outcomes. These principles are generic. Having more criteria on which to base decisions is not the issue. The important issue is data, and this is where the insurers can start helping. We have looked at technologies that are already in existence and concluded that we spend a fortune on many things about which we know nothing. There have been no trials. So insurers should start supporting clinical trials on technologies already in use.

We are paying now, so the additive dollars will be minimal. Thus, we just cannot eliminate an existing treatment because there are no studies. What we can do is conduct the clinical trial to see if there is value in the treatment or conditions under which its use is medically justified.

We need an authoritative body on medical technology assessments. We have the FDA, but it is a good source only for drugs. It has a limited authority for devices, and we have no authority for medical procedures.

Actually, when you think about this scientific work, it is interesting that the insurers are doing it. We do this kind of work because we have no other sources to which we can turn. We have sources on drugs but not for other treatments.

The insurers' administrative costs incorporate technology assessments. At Blue Cross/Blue Shield, it costs $30,000 to do one technology assessment, which is probably the going rate or somewhat lower. The commercial insurers such as Prudential, Aetna, and CIGNA also perform technology assessments. We are frequently assessing the same technologies. Recently, we have been talking about pooling our resources to fund common technology assessments. It would be much more efficient. That is one of the things that insurers can do, and we will be moving forward.

Finally, I would like to reiterate that I do not think the issue is whether something is investigational or whether investigational is on a continuum. The insurer must have a process that ultimately concludes whether something will be covered or not.

We are payers. What you want to hear is, yes, we are paying; no, we are not paying. You do not want to hear maybe we will pay. You do not want to hear that we are looking at it. So we must have a cutoff point.

I hope that I have clarified what we mean by investigational. Our dialogue should separate what is investigational from what is general practice and should be reimbursed. They are two different concepts that should not be distorted for payment purposes. It would be very appropriate to say that you think all investigational procedures should be covered. This is different from saying that a particular procedure should or should not be classified as investigational.

I would like to see the next conference address who should pay for medical research. We all have a responsibility, and it is one of those issues that must be addressed. Focusing on what is experimental or investigational is not the issue.

Discussion/Questions and Answers – Session 5

Comment: [Dr. Holohan] I agree with the basic principles of Ms. Gleeson's remarks, but if the question is "what is appropriate care?" we should have the same arguments about the definition of "appropriate" that we have about "investigational" or "experimental." I am not sure that particular word is the issue.

Q: [Peter Rheinstein, M.D., J.D., Food and Drug Administration] I have a question for Ms. Gleeson. Does your nonacceptance of Food and Drug Administration (FDA) device approval as a criteria for reimbursement extend only to the 510Ks or to the premarketing approvals (PMAs) as well?

A: [Ms. Gleeson] It applies to both. With the PMA, the companies have shown the FDA much more information on safety and effectiveness, and we frequently request that information from the FDA so we do not conduct the same investigations. The only reason at that point that a PMA is not automatically covered is because of criterion 4, where we want to know if it is as effective as the existing alternative, so we do that comparison; a PMA can go from criterion 1 all the way to criterion 4 and be evaluated there. But with the 510Ks, we do not accept that as a criterion for coverage.

Q: [Dr. Holohan] Dr. Rheinstein, will you explain what a 510K is?

A: [Dr. Rheinstein] 510K is a finding of substantial equivalence to a device that was in the marketplace prior to 1976. The law does not require any demonstration of safety or efficacy. Essentially, it is just a finding of "as effective as" and not "less safe than."

Q: [Marvin Shapiro, M.D., Medical Consultant, Los Angeles, CA] I have a question for Ms. Hummel. If I understood correctly, Medicare would not cover an autologous bone marrow transplant, which is an impressively expensive procedure, but would cover the complications stemming from it, which are even more expensive. If I am right, how does the Health Care Financing Administration (HCFA) justify that position and what is the rationale behind it?

A: [Ms. Hummel] Again, it is important to point out that cost is not necessarily the consideration. Our policy has been that when the sole purpose for admission to a hospital is for a noncovered service, then all of the ancillary services provided are also not covered. What evolves from a complication that may arise from investigational therapy, however, is a medically necessary or covered hospital admission as a result of whatever complication took place. Therefore, the cost of that care would be covered because the hospital admission and the medical necessity of the patient's condition would warrant hospitalization. The fact that it may end up costing more than the cost of the care for the investigational therapy is coincidental. That is not a consideration.

Q: [Dr. Shapiro] Ms. Gleeson, what is the position of Blue Cross/Blue Shield on complications of investigational procedures?

A: [Ms. Gleeson] Many of the plans are autonomous and have different approaches. The majority, though, exclude in their contracts the complications resulting from an investigational procedure.

Q: [Holly Dawkins, Institute of Medicine] Ms. Hummel, I found your presentation very useful. Is it HCFA's rock–bottom mission to protect the trust funds or is it to provide care that meets a certain basic level of qualifying criteria?

A: [Ms. Hummel] Most importantly, we pay for care through a trust fund mechanism, and in expending the trust funds, it is vital that we pay for quality care—we pay for the best care that we can get for our beneficiaries. In looking at that, we want to make sure that what they get works, that there is some proven safety and efficacy so that the quality of the care is, in fact, proven. In terms of "protecting the trust fund," we try to expend our financial resources the best way we can so that our beneficiaries have the best care they can get.

Q: [Dennis Cotter, Medical Technology and Practice Patterns Institute] I have a question for Ms. Gleeson. Have you ever gone through one of your technology assessments, either one in process or completed, and been challenged legally for those assessments where you decided not to cover, and have you reversed your position because of that legal challenge?

A: [Ms. Gleeson] I should probably begin by explaining that I am with the association, not with the plan. At the association, we do not have any contracts or deny coverage, so we cannot be sued for that. Plans could use our information, and they could be sued. At the association, we were sued for an antitrust violation. The particular device was investigational. No, we did not change our position as a result of the suit. The suit was settled, and there was no financial settlement.

Comment: [J. Jarrett Clinton, M.D., Administrator, Agency for Health Care Policy and Research] In closing, I am very appreciative of the time and effort that many of you have made both to be here and to contribute. We have demonstrated again that the Agency of Health Care Policy and Research can bring folks together who would not normally discuss a specific health care system issue, and we gain from it. The idea that this may lead to some other gathering is probably a correct one, and we will assess this information and would welcome hearing from you privately or publicly on whether you think we need to come together again at some future date. Thank you very much for being here.

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16. Abstract (Limit: 200 words)

When a new health care technology is developed, it must move along a continuum from experimental to state-of-the-art before it becomes available outside of investigational settings. A number of factors affect its progress in moving along the continuum. These include: evidence supporting its safety, effectiveness, and efficacy; the quality of the evidence; the existence of an already established technology with comparable benefits, risks, and costs; approval by regulatory agencies; public/practitioner pressure; and many others. Third-party papers usually will not provide reimbursement for the use of an experimental technology, and this has led in some cases to legal action. There is no clear definition of the terms "experimental" and "state-of-the-art" as they are used to describe health care technologies; rather, the definition often depends on the perspective from which a new technology is being described. This volume summarizes the presentations and floor discussion/questions and answers from a conference convened by the Agency for Health Care Policy and Research in November 1991 to examine this topic from a wide variety of viewpoints, including: ethical, legal, minority, NIH, medical colleges, practitioners, Food and Drug Administration, manufacturers, pharmaceutical, medical device, users, voluntary hospitals, Capitol Hill, and payers. Suggestions for new approaches to technology definition are discussed.

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